Associations of Herbal and Specialty Supplements with Lung and Colorectal Cancer Risk in the VITamins And Lifestyle Study

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Abstract

Millions of Americans use dietary supplements with little knowledge about their benefits or risks. We examined associations of various herbal/specialty supplements with lung and colorectal cancer risk. Men and women, 50 to 76 years, in the VITamins And Lifestyle cohort completed a 24-page baseline questionnaire that captured duration (years) and frequency (days per week) of use of commonly used herbal/specialty supplements. Dose was not assessed due to the lack of accurate potency information. Supplement exposure was categorized as ''no use'' or ''any use'' over the previous 10 years. Hazard ratios (HR) were estimated by multivariate Cox regression models. Incident lung (n = 665) and colorectal cancers (n = 428) were obtained from the Surveillance, Epidemiology, and End Results cancer registry. Any use of glucosamine and chondroitin, which have anti-inflammatory properties, over the previous 10 years, was associated with significantly lower lung cancer risk: HR 0.74 [95% confidence interval (95% CI), 0.58-0.94] and HR 0.72 (95% CI, 0.54-0.96) and colorectal cancer risk: HR 0.73 (95% CI, 0.54-0.98) and HR 0.65 (95% CI, 0.45-0.93), respectively. There were also statistically significantly inverse associations of fish oil: HR 0.65 (95% CI, 0.42-0.99), methylsulfonylmethane: HR 0.46 (95% CI, 0.23-0.93), and St. John's wort: HR 0.35 (95% CI, 0.14-0.85) with colorectal cancer risk. In contrast, garlic pills were associated with a statistically significant 35% elevated colorectal cancer risk. These results suggest that some herbal/specialty supplements may be associated with lung and colorectal cancer risk; however, these products should be used with caution. Additional studies examining the effects of herbal/specialty supplements on risk for cancer and other diseases are needed. (Cancer Epidemiol Biomarkers Prev 2009;18(5):1419–28)

Introduction

There has been a substantial increase in the use of complementary and alternative medicines, including dietary supplements, in the United States since the early 1990s (1-5). In particular, use of herbal or other nonvitamin, nonmineral ''specialty'' supplements has increased more than use of any other complementary and alternative medicine modality (1-6). This increased use is reflected both in sales figures and in self-reported use by the general population. For example, sales of dietary supplements increased from $8.8 billion in 1994 to $18.8 billion in 2003 (4, 5); in 2001 alone, Americans spent $4.2 billion on herbs and other botanical remedies (7). Kelly et al. (4) reported that in any week in 2002, 18.8% of American adults used a dietary supplement containing an herbal or other natural product. Based on recent trends, analysts predict that use of these supplements will continue to increase (1-8).

Millions of Americans are using these herbal and specialty formulations to prevent or treat diseases, with very limited evidence of their benefits or risks (3-6, 8-12). Passage of the Dietary Supplement Health and Education Act of 1994 established that dietary supplements (including herbal and specialty supplements) be regulated under a Food and Drug Administration category separate from both foods and drugs; thus, these products undergo minimal regulation (12, 13). Consequently, there are ongoing concerns about their safety (12-17). There are also concerns about their efficacy, given that relatively few randomized clinical trials have been conducted to assess their effects on risk for various diseases (12, 18). In addition, virtually no observational studies have examined whether use of these supplements is associated with risk for developing (or preventing) disease. Moreover, it is possible that these supplements may increase disease risk.

There have been several reports examining trends, patterns, motivations, as well as correlates and predictors of herbal and specialty supplement use in the general

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population and persons with cancer (1-6, 8-12, 14, 17, 19, 20). Studies have found that consumers use herbal and specialty supplements with the hope of preventing diseases, including cancers (3-6, 8-12, 19, 20). Lung and colorectal cancers are the second and third most common cancers in the United States, and the first and third leading causes of cancer deaths, respectively (21, 22). Several *in vitro*, cellular, and animal studies have evaluated the effects of herbal and other specialty products on the development and progression of lung and colorectal cancers (23-27); however, we are not aware of any comparable epidemiologic studies. Clearly, well-designed studies in human populations are critical to determining the potential effectiveness and/or adverse events associated with use of these products by consumers.

In this report, we examine associations of use of the most commonly used herbal and specialty supplements with risk of lung and colorectal cancers using data from a large cohort study of dietary supplements and cancer risk.

Materials and Methods

The VITamins And Lifestyle Study Recruitment and Response Rates. The VITamins And Lifestyle (VITAL) study aimed to investigate associations of dietary supplement use with cancer risk. Details of the study design and methods have been published (28). Cohort members were men and women ages 50 to 76 years at entry living in a 13-county area in western Washington State, the catchment area of the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) cancer registry, who completed a 24-page baseline questionnaire. Recruitment was conducted from October 2000 to December 2002.

Using names purchased from a commercial mailing list, 364,418 baseline questionnaires were mailed, followed by a post-card reminder after 2 weeks. Of the questionnaires, 79,300 were returned (21.8% overall, 19.5% response proportion among men, and 24.4% among women), of which 1,580 were ineligible and 241 failed quality control checks, leaving 77,719 eligible cohort members at baseline (28). The study protocol was approved by the institutional review board of the Fred Hutchinson Cancer Research Center (Seattle, WA).

Data Collection. Data were self-reported using a 24-page sex-specific, optically scanned questionnaire that covered three content areas: supplement use, diet, and health history and risk factors.

Measurement of Herbal and Specialty Supplement Use. Respondents were asked about use (duration in years, frequency in days per week, and usual dose) of various supplements, including multivitamins, individual vitamin and mineral supplements, other mixtures, and herbal and specialty products, during the 10 years before baseline. Details on the validity of assessment of multivitamin and individual vitamin and mineral supplement use have been published (29).

Participants reported on use of 20 herbal and specialty supplements from pills, tinctures, powders, and teas taken regularly (at least once a week for a year) during the previous 10 years: 16 products taken by men and women, as well as 2 for men only (DHEA and saw palmetto) and 2 for women only (black cohosh and dong quai). A closed-ended format was used to inquire about current versus past use, duration of use (1-2, 3-5, 6+ years), and frequency (1-2, 3-5, 6+ days per week) over the previous 10 years. Questions on dose were not included because of lack of accurate information on potency. Also, respondents could report on use of herbal and specialty supplements in the multivitamin section, as some of the multivitamins queried on included herbal products.

For these analyses, due to limited distribution based on years of use (1-2, 3-5, 6+), herbal and specialty supplement exposure was categorized as ''no use'' or ''any use'' over the over the previous 10 years, based on use reported from individual supplements, mixtures, and multivitamins when indicated. Only the 11 herbal and specialty supplements for which at least 5% of participants were users were included.

Other Participant Characteristics and Covariates. The questionnaire captured numerous covariates, including demographic and lifestyle characteristics, health history, medication use with emphasis on nonsteroidal anti-inflammatory drugs (NSAID) use, physical activity over the 10 years before baseline, cancer screening practices, and other potential confounders of supplement-cancer associations. In these analyses, we considered adjustment for sociodemographic characteristics (self-reported age, sex, race, and education); lifestyle and behavioral factors (smoking history, physical activity, fruit and vegetable consumption, use of nonfiber laxatives); and anthropometric characteristics [weight, height, and body mass index (BMI, kg/m^2)]. Prior history of cancer, first-degree family history of lung or colorectal cancer, sigmoidoscopy/colonoscopy use, self-report of physician-diagnosed chronic obstructive pulmonary disease (COPD) and/or asthma, and having had a polyp removed were also obtained.

Smokers were defined as individuals who smoked at least one cigarette per day for at least a year and smoking status was defined as never, current, quit 10 years or more, or quit less than 10 years ago, as of the date of questionnaire completion. Duration of smoking was estimated by the reported number of years smoked and intensity by the usual number of cigarettes smoked per day.

Outcome Assessment. Participants were followed for lung and colorectal cancers occurring from baseline through December 31, 2006, by linking the cohort to the Seattle-Puget Sound SEER registry. Cases are captured through all hospitals in the area, offices of pathologists, oncologists, and radiotherapists, and from State death certificates. Cancer cases were identified in the cohort using matching algorithms on personal identifiers and human review (28).

For each participant, the censored date was the earliest date of withdrawal from the study (0.03%), death (3.02%), move out of the SEER catchment area (4.57%), or last date of linkage to the SEER registry for remaining participants (December 31, 2006). Deaths were ascertained by linkage to Washington State death files, and moves out of the area were identified through the National Change of Address System and by follow-up letters and telephone calls. If a participant had multiple diagnoses of lung or colorectal cancer, we used the time to first primary diagnosis.

For these analyses, we excluded 588 and 1,184 participants with a self-reported history of lung cancer and colorectal cancer, respectively, at baseline (or who did not complete the baseline medical history section); 2 individuals whose lung cancer was classified as lymphoma; 23 colorectal cancers with morphologies of large cell/squamous cell/Goblet cell carcinoma, carcinoid tumor, neuroendocrine carcinoma or lymphoma; and 4 lung cancer cases who diagnoses was based on death certificate only, leaving 665 lung cancer cases and 76,460 non–lung cancer cases and 428 colorectal cancer cases and 76,084 noncolorectal cancer cases.

Statistical Analysis. Data analyses were done using SAS (version 9.1, 2002-2003, SAS Institute, Inc.). Cox proportional hazards regression was used to estimate the hazard ratios (HR) for associations of the herbal and specialty supplements with lung and colorectal cancer risk. Robust SEs were used to eliminate traditional proportional hazards assumptions.

Lung Cancer Analyses. A priori and using a stepwise procedure, we analyzed variables that measured smoking status, duration, and intensity [pack-years, pack-years squared, years of smoking, years of smoking squared, smoking status (four categories as above), and age when started smoking] in a Cox model predicting lung cancer risk at a $P = 0.05$ level. Our final model included years smoked, pack-years, and a squared pack-years term. We also decided a priori to include age and gender in the model. Finally, we evaluated whether education (≤high school, some college, college graduate), physical activity (quartiles), BMI (underweight, normal, overweight, obese), fruit and vegetable consumption (quartiles), previous history of cancer (yes, no), COPD/emphysema/asthma (yes, no), and first-degree family history of lung cancer (yes, no) were confounders of the herbal/specialty supplement-lung cancer associations in models already adjusted for age, gender, and the smoking variables. These factors did not seem to confound associations of the other herbal and specialty products; thus, the more parsimonious models were used. For glucosamine and chondroitin, we further adjusted for NSAID use (4+ times per week for 4+ years, yes or no), current multivitamin use (yes, no), and history of arthritis (yes, no), as these supplements are often used by persons with osteoarthritis (30).

Colorectal Cancer Analyses. We evaluated whether education, physical activity, smoking status, BMI, fruit and vegetable consumption, use of nonfiber laxatives (never/<1 per year, 1-4 times per year, 5-11 times per year, 1-3 times per month, ≥1 time per week), NSAID use, sigmoidoscopy use in the past 10 years (yes, no), current multivitamin use, previous history of cancer, and first-degree family history of colorectal cancer (yes, no) were confounders of the herbal/specialty supplement-colorectal cancer associations in models already adjusted for age and gender. The final model for all the herbal and specialty supplements included age, gender, education, physical activity, BMI, fruit and vegetable consumption, NSAID use, and sigmoidoscopy. Glucosamine, chondroitin, and methylsulfonylmethane (MSM) were further adjusted for history of arthritis.

For both lung and colorectal cancers, glucosamine, chondroitin, and MSM were also adjusted for each of the other two supplements, as these three compounds are often marketed to be taken together (30). These adjustments did not change the results appreciably; thus, the results presented do not reflect adjustment for these supplements. Also, adjusting associations of St. John's wort with colorectal cancer for depression (an indication for using the supplement) did not change the results. Finally, excluding participants whose cancer was diagnosed within the first year of follow-up did not change the results; thus, the entire study sample was included.

Results

More than 77,000 VITAL cohort participants ($n = 77,125$ for lung cancer and $n = 77,512$ for colorectal cancer) met the inclusion criteria for these analyses and were followed for a mean of 5.0 years (SD 1.01 years). Six hundred and sixty-five participants developed lung cancer, of which 391 (75%) were non–small cell lung cancer (NSCLC). Fourteen percent were small-cell lung cancer (SCLC) and the remaining cancers (11%) included carcinomas not otherwise specified and carcinoid/neuroendocrine tumors. Of the NSCLC, 34% were adenocarcinoma ($n = 226$), 17% were squamous cell ($n = 116$), 2% were large cell ($n = 16$), and 22% were NSCLC, not otherwise specified ($n = 143$).

Table 1 gives demographic and other characteristics of lung cancer cases and non–lung cancer cases. Relative to noncases, participants with lung cancer were more likely to be older (67.2 versus 61.9 years); male (55% versus 48%); have a high school education or lower (37% versus 20%); be current smokers (31% versus 8%); sedentary (24% versus 15%); consume fewer fruits and vegetables; be NSAID users (34% versus 26%); have had a prior cancer (30% versus 20%), COPD/emphysema (17% versus 3%), and a family history of lung cancer (20% versus 13%); but were less likely to be obese (19% versus 25%). There were no differences in current use of multivitamins or history of arthritis.

As shown in Table 2, colorectal cancer cases tended to be older (66.3 vs. 61.9 years), non-college graduates (31% vs. 42%), never smokers (39% vs. 48%), obese (30% vs. 25%), and use non-fiber laxatives more frequently (14% vs. 9% at 1-4 times per year), but were less likely to have obtained a sigmoidoscopy in the previous 10 years (45% vs. 57%). There were no clear differences based on gender, smoking status, physical activity, consumption of fruits/vegetables, NSAID use, current multivitamin use, having had a polyp removed, arthritis, or family history of colorectal cancer.

Associations of use of various herbal and specialty supplements with lung cancer risk are given in Table 3. Any use of glucosamine and chondroitin during the previous 10 years was statistically significantly inversely associated with lung cancer risk: HR 0.74 (95% CI, 0.58-0.94; $P = 0.01$) and HR 0.72 (95% CI, 0.54-0.96; $P = 0.02$), respectively. These associations persisted after control for the main adjustment factors in Table 1 (age, gender, education, smoking) as well as history of arthritis (the main indication for glucosamine and chondroitin use), NSAID use (another common treatment for arthritis), and current multivitamin use. Associations with total lung cancer were comparable for NSCLC but were stronger for adenocarcinomas: HR 0.61 (95% CI, 0.41-0.92;

Table 1. Participant characteristics of lung cancer cases and non–lung cancer cases, the VITAL Study (*n* = 77,125)

Characteristic	Lung cancer cases (*n* = 665)	Controls* (*n* = 76,460)
Age at baseline (y), *n* (%)		
50-59	116 (17)	35,269 (46)
60-69	274 (41)	26,481 (35)
≥70	275 (41)	14,710 (19)
Mean ± SD	67.2 (6.6)	61.9 (7.4)
Gender, *n* (%)		
Female	296 (45)	39,777 (52)
Male	369 (55)	36,683 (48)
Race, *n* (%)		
Non-White	37 (6)	5,138 (7)
White	609 (94)	70,009 (93)
Education, *n* (%)		
≤High school education	237 (37)	15,022 (20)
Some college	259 (40)	28,776 (38)
College graduate/advanced degree	152 (23)	31,369 (42)
Smoking status, *n* (%)		
Never	52 (8)	36,389 (48)
Former, quit ≥10 y	275 (42)	28,091 (37)
Former, quit <10 y	128 (19)	4,906 (6)
Current	203 (31)	6,220 (8)
Pack-years of cigarettes (mean ± SD)	43.4 (27.7)	13.3 (21.0)
No. years as a smoker, *n* (%)		
Nonsmokers (0-0)	52 (8)	36,389 (48)
Lower half of smokers (2.5-24.5)	50 (8)	17,827 (24)
Upper half of smokers (25-59)	556 (84)	21,482 (28)
Mean (SD)	33.8 (13.9)	11.8 (14.9)
Physical activity (MET-h/wk)		
No exercise	157 (24)	11,245 (15)
1st Quartile (0.01-3.03)	145 (22)	16,034 (21)
2nd Quartile (3.04-8.06)	148 (23)	15,998 (21)
3rd Quartile (8.07-17.81)	107 (16)	16,057 (21)
4th Quartile (>17.81)	92 (14)	16,073 (21)
BMI category (kg/m^2)		
Underweight (<18.5)	16 (3)	652 (1)
Normal (18.5-24.9)	230 (37)	24,334 (33)
Overweight (25-29.9)	262 (42)	29,796 (41)
Obese (≥30)	120 (19)	17,902 (25)
Vegetables (servings/d)		
1st Quartile (0-1.33)	171 (30)	17,242 (25)
2nd Quartile (1.34-1.97)	151 (26)	17,231 (25)
3rd Quartile (1.98-2.88)	139 (24)	17,315 (25)
4th Quartile (>2.88)	110 (19)	17,296 (25)
Fruit (servings/d)		
1st Quartile (0-0.75)	200 (35)	17,206 (25)
2nd Quartile (0.76-1.34)	132 (23)	17,274 (25)
3rd Quartile (1.35- 2.31)	133 (23)	17,281 (25)
4th Quartile (>2.31)	104 (18)	17,313 (25)
NSAID use (4+ times/wk, 4+ y), *n* (%)		
No	430 (66)	55,070 (74)
Yes	222 (34)	19,772 (26)
Current use a multivitamin, *n* (%) †		
No	291 (44)	32,245 (42)
Yes	374 (56)	44,205 (58)
Medical history, *n* (%)		
Prior cancer		
No	461 (70)	61,188 (80)
Yes	202 (30)	15,272 (20)
COPD or emphysema		
No	549 (83)	73,809 (97)
Yes	114 (17)	2,633 (3)
Arthritis		
No	452 (68)	53,739 (70)
Yes	211 (32)	22,703 (30)
Family history of lung cancer, *n* (%) ‡		
No	526 (80)	65,962 (87)
Yes	131 (20)	9,495 (13)

NOTE: All characteristics had <5% missing data and percentages are of the total. Numbers may not sum to the total and percentages may not add up to 100% because of missing data and/or rounding.

*Controls refer to the non–lung cancer cases.

† Multivitamin users who responded ''sometimes'' were included in the ''yes'' category.

‡ Family history of colorectal cancer was defined as one or more first-degree relative with lung cancer.

Table 2. Participant characteristics of colorectal cancer cases and noncolorectal cancer cases, the VITAL Study (*n* = 76,512)

Characteristic	Colorectal cancer cases (*n* = 428)	Controls* (*n* = 76,084)
Age at baseline (y), *n* (%)		
50-59	87 (20)	35,185 (46)
60-69	190 (44)	26,336 (35)
≥70	151 (35)	14,563 (19)
Mean ± SD	66.3 (6.7)	61.9 (7.4)
Gender, *n* (%)		
Female	208 (49)	39,568 (52)
Male	220 (51)	36,516 (48)
Race, *n* (%)		
Non-White	37 (9)	5,083 (7)
White	383 (91)	69,964 (93)
Education, *n* (%)		
≤High school education	143 (34)	14,969 (20)
Some college	146 (35)	28,679 (38)
College graduate/advanced degree	132 (31)	31,142 (42)
Smoking status, *n* (%)		
Never	163 (39)	35,922 (48)
Former, quit ≥10 y	182 (43)	27,933 (37)
Former, quit <10 y	36 (9)	5,025 (7)
Current	41 (10)	6,352 (8)
Physical activity (MET-h/wk)		
No exercise	68 (16)	11,245 (15)
1st Quartile (0.01-3.02)	105 (25)	15,947 (21)
2nd Quartile (3.03-8.06)	92 (22)	15,928 (21)
3rd Quartile (8.07-17.81)	72 (17)	15,958 (21)
4th Quartile (>17.81)	78 (19)	15,959 (21)
BMI category (kg/m^2)		
Underweight (<18.5)	8 (2)	656 (1)
Normal (18.5-24.9)	112 (28)	24,296 (34)
Overweight (25-29.9)	160 (40)	29,636 (41)
Obese (≥30)	122 (30)	17,747 (25)
Vegetables (servings/d)		
1st Quartile (0-1.33)	102 (27)	17,151 (25)
2nd Quartile (1.34-1.97)	105 (28)	17,168 (25)
3rd Quartile (1.98-2.88)	86 (23)	17,220 (25)
4th Quartile (>2.88)	81 (22)	17,179 (25)
Fruits (servings/d)		
1st Quartile (0-0.75)	98 (26)	17,178 (25)
2nd Quartile (0.76-1.34)	98 (26)	17,177 (25)
3rd Quartile (1.35-2.31)	105 (28)	17,157 (25)
4th Quartile (>2.31)	72 (19)	17,197 (25)
Use of nonfiber laxatives		
Never/<1/y	315 (81)	60,856 (86)
1-4 times/y	53 (14)	6,192 (9)
5-11 times/y	12 (3)	1,858 (3)
1-3 times/mo	7 (2)	924 (1)
≥1 time/wk	3 (1)	732 (1)
NSAID use (4+ times/wk, 4+ y), *n* (%)		
No	321 (77)	54,748 (74)
Yes	94 (23)	19,736 (26)
Sigmoidoscopy/colonoscopy in the past 10 y, *n* (%)		
No	232 (55)	32,641 (43)
Yes	191 (45)	42,794 (57)
Current use a multivitamin, *n* (%) †		
No	182 (43)	32,100 (42)
Yes	246 (57)	43,974 (58)
Medical history, *n* (%)		
Prior cancer		
No	312 (73)	61,322 (81)
Yes	116 (27)	14,762 (19)
Polyp removed from colon		
No	370 (86)	66,406 (87)
Yes	58 (14)	9,678 (13)
Arthritis		
No	300 (70)	53,469 (70)
Yes	128 (30)	22,598 (30)
Family history of colorectal cancer, *n* (%) ‡		
No	354 (85)	66,534 (89)
Yes	63 (15)	8,556 (11)

NOTE: All characteristics had <5% missing data and percentages are of the total. Numbers may not sum to the total and percentages may not add up to 100% because of missing data and/or rounding.

*Controls refer to the noncolorectal cancer cases.

† Multivitamin users who responded ''sometimes'' were included in the ''yes'' category.

‡ Family history of colorectal cancer was defined as one or more first-degree relative with colorectal cancer.

Table 3. Associations of lung cancer risk with use of various herbal and specialty supplements during the previous 10 y, the VITAL Study (*n* = 77,125)

Herbal or specialty supplement*	Lung cancer cases (*n* = 665), *n* (%)	Non–lung cancer cases (*n* = 76,460), *n* (%)	Adjusted HR † (adjusted 95% CI †)
Fish oil			
No use	608 (91)	68,760 (90)	1.00 (Reference)
Any pills per day during the previous 10 y	57 (9)	7,453 (10)	1.09 (0.83-1.44)
User vs non-user *P*			0.52
Garlic pills			
No use	582 (88)	67,204 (88)	1.00 (Reference)
Any pills per day during the previous 10 y	80 (12)	8,950 (12)	1.05 (0.83-1.34)
User vs non-user *P*			0.66
Gingko biloba			
No use	584 (88)	65,753 (86)	1.00 (Reference)
Any pills per day during the previous 10 y	80 (12)	10,411 (14)	1.04 (0.82-1.32)
User vs non-user *P*			0.76
Ginseng			
No use	620 (94)	69,888 (92)	1.00 (Reference)
Any pills per day during the previous 10 y	43 (6)	6,322 (8)	0.97 (0.70-1.33)
User vs non-user *P*			0.93
Grapeseed			
No use	631 (95)	70,512 (92)	1.00 (Reference)
Any pills per day during the previous 10 y	33 (5)	5,786 (8)	0.97 (0.68-1.38)
User vs non-user *P*			0.86
Glucosamine ‡			
No use	576 (87)	60,733 (80)	1.00 (Reference)
Any pills per day during the previous 10 y	88 (13)	15,458 (20)	0.74 (0.58-0.94)
User vs non-user *P*			0.01
Chondroitin ‡			
No use	609 (92)	65,789 (86)	1.00 (Reference)
Any pills per day during the previous 10 y	55 (8)	10,368 (14)	0.72 (0.54-0.96)
User vs non-user *P*			0.02
Melatonin			
No use	638 (96)	72,449 (95)	1.00 (Reference)
Any pills per day during the previous 10 y	26 (4)	3,799 (5)	0.99 (0.66-1.47)
User vs non-user *P*			0.95
MSM			
No use	636 (96)	72,640 (95)	1.00 (Reference)
Any pills per day during the previous 10 y	29 (4)	3,675 (5)	1.00 (0.68-1.47)
User vs non-user *P*			0.99
St. John's wort			
No use	638 (96)	72,375 (95)	1.00 (Reference)
Any pills per day during the previous 10 y	24 (4)	3,868 (5)	0.98 (0.65-1.48)
User vs non-user *P*			0.94
Saw palmetto §			
No use	335 (90)	32,564 (89)	1.00 (Reference)
Any pills per day during the previous 10 y	34 (10)	4,043 (11)	0.84 (0.59-1.21)
User vs non-user *P*			0.36

NOTE: Only herbal or specialty supplements for which at least 5% of either cases or noncases were users are included. Numbers may not sum to the total and percentages may not add up to 100% because of missing data and/or rounding.

*Based on self-reported intakes from the individual supplements, mixtures, and multivitamins, when relevant.

† Adjusted for age, gender, education, years smoked, pack-years, and pack-years squared.

‡ Adjusted for age, gender, education, years smoked, pack-years, pack-years squared, NSAID use, history of arthritis, and multivitamin use. Also, glucosamine, chondroitin, and MSM were adjusted for each of the other two supplements.

§ Saw palmetto was asked of men only.

P = 0.02) and HR 0.50 (95% CI, 0.30-0.84; *P* = 0.009) for glucosamine and chondroitin, respectively (data not shown in the table). No other herbal or specialty supplements were associated with lung cancer risk.

Table 4 gives associations of any use of herbal or specialty supplement use over the previous 10 years with colorectal cancer risk. The strongest associations were for St. John's wort (HR, 0.35; 95% CI, 0.14-0.85; *P* = 0.02) and MSM (HR, 0.46; 95% CI, 0.23-0.93; *P* = 0.03) with colorectal risk. Associations were also statistically significant for fish oil (HR, 0.65; 95% CI, 0.42-0.99; *P* = 0.05), glucosamine (HR, 0.72; 95% CI, 0.54-0.98; *P* = 0.03), and chondroitin (HR, 0.65; 95% CI, 0.45-0.93; *P* = 0.02) supplements. In contrast, use of garlic pills was associated with a significant 35% elevated risk (HR, 1.35; 95% CI, 1.01-1.81; *P* = 0.04). Melatonin was associated with a nonstatistically significant 42% reduced risk. No other herbal or specialty supplements were associated with colorectal cancer risk.

Discussion

In this study that examined whether use of various herbal and specialty supplements were associated with risk for lung and colorectal cancers, any use of glucosamine and chondroitin supplements in the previous

10 years were associated with significantly lower risk for both cancers. In addition, use of fish oil, St. John's wort, melatonin, and MSM supplements were associated with 35% to 65% reductions in colorectal rectal cancer risk, whereas garlic pills were associated with significantly elevated risk. Because, to our knowledge, there are no observational studies of glucosamine, chondroitin, or MSM, and very few of garlic or fish oil in relation to lung and colorectal cancer risk in human populations, this makes it challenging to place our findings in the context of the current body of knowledge.

We were somewhat surprised by the consistent inverse associations of glucosamine and chondroitin with lung and colorectal cancer risk, which persisted even after control for various demographic and lifestyle factors and health conditions that may be confounders. Glucosamine is made from glucose and the amino acid glutamine, used in the formation and repair of cartilage and other body tissues, and found naturally in the body; its production, however, slows with age (31-35). Glucosamine is commonly taken in combination with chondroitin, a glycosaminoglycan derived from articular cartilage. Like glucosamine, chondroitin may prevent the breakdown of cartilage, and research studies (including some randomized trials) suggest that both compounds may also be effective treatments for osteoarthritis (31-36).

Table 4. Associations of colorectal cancer risk with use of various herbal and specialty supplements during the previous 10 y, the VITAL Study (n = 76,512)

Herbal or specialty supplement*	Colorectal cancer cases (n = 428), n (%)	Noncolorectal cancer cases (n = 76,084), n (%)	Adjusted hazard ratio [†] (adjusted 95% CI [†])
Fish oil			
No use	399 (93)	68,417 (90)	1.00 (Reference)
Any pills per day during the previous 10 y	28 (7)	7,424 (10)	0.65 (0.42-0.99)
User vs non-user P			0.05
Garlic pills			
No use	358 (84)	66,893 (88)	1.00 (Reference)
Any pills per day during the previous 10 y	70 (16)	8,883 (12)	1.35 (1.01-1.81)
User vs non-user P			0.04
Gingko biloba			
No use	377 (88)	65,146 (86)	1.00 (Reference)
Any pills per day during the previous 10 y	49 (12)	10,373 (14)	0.83 (0.59-1.17)
User vs non-user P			0.29
Ginseng			
No use	397 (93)	69,528 (92)	1.00 (Reference)
Any pills per day during the previous 10 y	29 (7)	6,309 (8)	0.86 (0.56-1.33)
User vs non-user P			0.50
Grapeseed			
No use	406 (95)	70,177 (92)	1.00 (Reference)
Any pills per day during the previous 10 y	22 (5)	5,746 (8)	0.72 (0.44-1.18)
User vs non-user P			0.19
Glucosamine [‡]			
No use	360 (85)	60,444 (80)	1.00 (Reference)
Any pills per day during the previous 10 y	66 (15)	15,373 (20)	0.73 (0.54-0.98)
User vs non-user P			0.03
Chondroitin [‡]			
No use	385 (90)	65,556 (86)	1.00 (Reference)
Any pills per day during the previous 10 y	42 (10)	10,316 (14)	0.65 (0.45-0.93)
User vs non-user P			0.02
Melatonin			
No use	410 (96)	72,080 (95)	1.00 (Reference)
Any pills per day during the previous 10 y	15 (4)	3,794 (5)	0.58 (0.30-1.13)
User vs non-user P			0.11
MSM [‡]			
No use	415 (97)	72,262 (95)	1.00 (Reference)
Any pills per day during the previous 10 y	13 (3)	3,678 (5)	0.46 (0.23-0.93)
User vs non-user P			0.03
St. John's wort			
No use	418 (98)	72,000 (95)	1.00 (Reference)
Any pills per day during the previous 10 y	8 (2)	3,866 (5)	0.35 (0.14-0.85)
User vs non-user P			0.02
Saw palmetto [§]			
No use	194 (88)	32,424 (89)	1.00 (Reference)
Any pills per day during the previous 10 y	26 (12)	4,017 (11)	1.01 (0.65-1.58)
User vs non-user P			0.97

NOTE: Only herbal or specialty supplements for which at least 5% of either cases or noncases were users are included. Numbers may not sum to the total and percentages may not add up to 100% because of missing data and/or rounding.

*Based on self-reported intakes from the individual supplements, mixtures, and multivitamins, when relevant.

[†] Adjusted for age, gender, education, physical activity, fruit and vegetable consumption, BMI, NSAID use, and sigmoidoscopy.

[‡] Adjusted for age, gender, education, physical activity, fruit and vegetable consumption, BMI, NSAID use, sigmoidoscopy, and history of arthritis. Also, glucosamine, chondroitin, and MSM were adjusted for each of the other two supplements.

[§] Saw palmetto was asked of men only.

Although these supplements are most commonly used by patients with osteoarthritis and have been studied extensively for purpose, they are not often considered potential preventive agents for cancer. Nonetheless, there are possible mechanisms by which these products may influence the carcinogenic process. There is evidence that glucosamine inhibits the interleukin-1 signaling cascade and gene expression. Specifically, glucosamine seems to inhibit both anabolic and catabolic genes; thus, its potential therapeutic effects (if any) might be due to anticatabolic activities, which can affect cancer development (31, 33-36). Both glucosamine and chondroitin also have anti-inflammatory properties (31, 33-36) and there is growing evidence that tissue damage caused by inflammation can initiate or promote the development of lung and colorectal cancers and that other anti-inflammatory drugs reduce the risk of both lung and colorectal cancer (37). The anti-inflammatory properties of these compounds are exhibited through diverse mechanisms such as reducing the expression of phospholipase A2, cyclooxygenase-2, and concentrations of prostaglandin E_2, reactive oxygen and nitrogen species, and proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6 (31, 33-36). *In vitro*, glucosamine sulfate has been shown to reduce prostaglandin E_2 production and interfere with nuclear factor-κB DNA binding in chondrocytes and synovial cells (31, 32-36, 38). We note that randomized clinical trials of glucosamine and osteoarthritis suggest that the sulfate moiety provides clinical benefit in the synovial fluid by strengthening cartilage and aiding glycosaminoglycan synthesis, which would indicate that the glucosamine sulfate (and not nonsulfated glucosamine) form is more effective (31-34). Most specialty formulations of glucosamine used by consumers are in sulfate form. Therefore, from a mechanistic perspective, it is plausible that glucosamine and chondroitin may reduce risk for lung and colorectal cancers through underlying mechanisms. However, additional studies examining these potential associations in human populations are needed.

MSM is a sulfur-containing compound normally found in food that is often marketed in combination with glucosamine and chondroitin (33, 39, 40). In the present study, MSM was associated with a significant (HR, 0.54) decrease in colorectal cancer risk, which was also unanticipated. It is chemically related to DMSO, a popular, although unproven, treatment for arthritis that has also been proposed as a treatment for cancer (39, 40). In fact, it has been suggested that the health benefits associated with DMSO may be due to MSM, which is a breakdown by-product of DMSO. Although there is scant support for these hypotheses, it has been suggested that DMSO, and by extension, MSM, interferes with cancer development by stimulating various parts of the immune system, scavenging free (hydroxyl) radicals, and inhibiting cell growth (39, 40). However, currently, there is no evidence that MSM is beneficial for cancer or any other health condition.

As in some other studies (41-43), melatonin was associated with a reduction in colorectal cancer risk (42% in the present investigation), although the association was not statistically significant. Melatonin is a hormone produced in the brain from the amino acid tryptophan. The synthesis and release of melatonin are stimulated by darkness and suppressed by light, and it is well-accepted that it is involved in regulatory control of the sleep/wake cycle, as well as circadian rhythms generally (42, 43). In addition, there is appreciable evidence indicating that melatonin is involved in preventing tumor initiation, promotion, and progression; these anticarcinogenic effects seem to be due to its antioxidant, immunostimulating, and apoptotic properties (41-43). In *in vitro* studies and animal models, melatonin has been shown to inhibit growth of breast, prostate, liver, hepatoma, and colorectal cancer cell lines (41-43). Moreover, melatonin secretion is impaired in patients with some cancers, including colorectal cancer, and it has been hypothesized that the somewhat higher incidence of colorectal cancer in persons who work the night shift may be due to lower secretion of melatonin and increased exposure to light during nighttime (41-43).

St. John's wort is one of the most investigated medicinal plants and is a member of the genus *Hypericum* (44). It has been extensively studied as an herbal treatment for depression; however, we are not aware of any human studies evaluating a potential link to cancer. Therefore, it is somewhat surprising that it was associated with a 65% decrease in risk for colorectal cancer. Potential mechanism(s) of action of St. John's are not known (44). Any anticarcinogenic activity may be due to antioxidant properties conferred by other biologically active constituents within the plant, such as flavonoids and tannins (44).

It is not unexpected that use of fish oil supplements was associated with a statistically significant 35% lowering of colorectal cancer risk, as they contain omega-3 fatty acids (n-3 PUFA), eicosapentaenoic acid, and docosahexaenoic acid, precursors to eicosanoids that reduce inflammation (45, 46). As noted above, uncontrolled inflammatory processes have been linked to elevated risk for colorectal cancer (37, 45, 46). In particular, a variety of experimental studies, clinical trials, and observational studies have substantiated a beneficial role of n-3 PUFAs in colorectal cancer, largely due to their regulatory roles in cell proliferation and apoptosis and their antiangiogenic and anti-inflammatory properties (37, 45, 46).

We were surprised, however, that garlic pills were associated with significantly elevated colorectal cancer risk, because animal studies and observational (cohort and case-control) studies have suggested a potentially protective role for garlic on colorectal cancer (26, 47-49). Also, a recent randomized clinical trial reported a significant suppression in both the total size and number of adenomas in colorectal cancer patients ($n = 37$) taking aged garlic extract (49). Any antitumor activities associated with garlic are believed to be due to its antioxidant properties (47-49). However, it is worth noting that whereas some human studies have shown inverse associations of garlic consumption with colorectal cancer risk, there is considerable heterogeneity in assessment/measures of garlic intake, types of garlic consumed (e.g., cooked, fresh, extract), and outcome (colorectal cancer, adenoma number and/or size).

Our study has several strengths. We used a comprehensive instrument that captured long-term use of 20 different herbal and specialty supplements. The assessment of (long-term) intake during the 10 years before baseline allowed us to more closely investigate herbal and specialty supplement exposure over the relevant

period of cancer development. Exposure and risk factor ascertainment were obtained before the diagnosis of cancer and this prospective approach reduced the likelihood of selection bias because potential participants could not choose to take part in the study based on both supplement use and future (unknown) cancer diagnosis. We controlled for several factors that affect or modify lung and colorectal cancer risk, particularly the strong effects of tobacco smoking (for lung cancer), lifestyle/behavioral factors and screening (for colorectal cancer), and the diseases that are common indications for use of certain supplements (i.e., confounding by indication). Finally, cancer cases were ascertained using a comprehensive linkage system with the SEER registry, which we have estimated to be almost 100% complete for the year 2006, suggesting that the number of nonidentified cases should be minimal.

The study also has some potential limitations. As with other observational studies, there is the possibility of uncontrolled or residual confounding. In addition, there is likely some misclassification due to self-report of supplement use, although this is unlikely to be differential in a cohort study. Finally, we did not have sufficient numbers of herbal or specialty supplement users who developed cancer to characterize use other than as no use versus use in the past 10 years.

In summary, this is one of the first observational epidemiologic studies to comprehensively and rigorously examine associations of several commonly used herbal and specialty supplements with risks for lung and colorectal cancers. Glucosamine and chondroitin use was associated with significantly reduced risk for both tumor types; St. John's wort, MSM, fish oil, and melatonin were inversely associated with colorectal cancer risk; and garlic pills were associated with higher risk. Although the results of this study are intriguing, possible risks associated with most herbal and specialty supplements are not known (14-17). For example, in theory, glucosamine may decrease the effectiveness of drugs that lower blood sugar levels and may increase risk of bleeding (31-34). The side effects of St. John's wort include gastrointestinal symptoms, anxiety, fatigue, and drug interactions (14, 17, 44). Therefore, these supplements should be recommended and used with caution. In addition, given their ever-growing popularity, additional human studies examining the possible effects of herbal and specialty supplements on risk for cancer and other health conditions are urgently needed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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