Glucosamine and Chondroitin Supplements and Risk of Colorectal Adenoma and Serrated Polyp

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ABSTRACT

Background: Studies have shown an inverse association between use of glucosamine and chondroitin supplements and colorectal cancer risk. However, the association with the precursor lesion, colorectal adenoma and serrated polyp, has not been examined.

Methods: Analyses include 43,163 persons from the Nurses' Health Study (NHS), Health Professionals Follow-up Study (HPFS), and NHS2 who reported on glucosamine/chondroitin use in 2002 and who subsequently underwent ≥1 lower gastrointestinal endoscopy. By 2012, 5,715 conventional (2,016 high-risk) adenomas were detected, as were 4,954 serrated polyps. Multivariable logistic regression for clustered data was used to calculate OR and 95% confidence intervals (CI).

Results: Glucosamine/chondroitin use was inversely associated with high risk and any conventional adenoma in NHS and HPFS: in the pooled multivariable-adjusted model, glucosamine + chondroitin use at baseline was associated with a 26% (OR = 0.74; 95% CI, 0.60–0.90; $P_{heterogeneity} = 0.23$) and a 10% (OR = 0.90; 95% CI, 0.81–0.99; $P_{heterogeneity} = 0.36$) lower risk of high-risk adenoma and overall conventional adenoma, respectively. However, no association was observed in NHS2, a study of younger women (high-risk adenoma: OR = 1.09; 95% CI, 0.82–1.45; overall conventional adenoma: OR = 1.00; 95% CI, 0.86–1.17), and effect estimates pooled across all three studies were not significant (high-risk: OR = 0.83; 95% CI, 0.63–1.10; $P_{heterogeneity} = 0.03$; overall conventional adenoma: OR = 0.93; 95% CI, 0.85–1.02; $P_{heterogeneity} = 0.31$). No associations were observed for serrated polyps.

Conclusions: Glucosamine/chondroitin use was associated with lower risks of high-risk and overall conventional adenoma in older adults; however, this association did not hold in younger women, or for serrated polyps.

Impact: Our study suggests that glucosamine and chondroitin may act on early colorectal carcinogenesis in older adults.

Introduction

Colorectal cancer is the third most common cancer among men and women in the United States (1). Therefore, it is critical to identify safe, effective, and easily implemented preventive strategies to reduce colorectal cancer incidence. Accumulating evidence suggests that inflammation plays an important role early in the etiology of colorectal cancer (2–7). Thus, reducing inflammation may offer a potential approach to blunting the process of colorectal carcinogenesis by preventing precursor adenomas, and reducing risk of colorectal cancer.

Glucosamine and chondroitin are among the most commonly used specialty supplements in the United States, with 3.4% of adults ages 40 to 64 years reporting use of glucosamine and 8.5% of adults aged 65+ years reporting use (8, 9). These nonvitamin, nonmineral supplements are often, but not always, taken in a single daily supplement for osteoarthritis. Although the effectiveness for joint pain and function remains debated (10–16), a growing body of literature suggests that these supplements may have chemopreventive potential against cancer. In an exploratory analysis conducted within the VITamins And Lifestyle (VITAL) prospective cohort, use of glucosamine and chondroitin was associated with reduced risk of colorectal cancer; specifically, use of glucosamine was associated with a 27% reduced risk of colorectal cancer and use of chondroitin was associated with a 35% reduced risk (17). More recently, three subsequent cohort studies consistently showed that use of glucosamine alone (18) or glucosamine + chondroitin (19, 20) was significantly associated with reduced risk of colorectal cancer. Moreover, a recent case–control study from the MCC-Spain Study observed a comparable effect estimate when comparing persons using glucosamine + chondroitin to nonusers, although power for this analysis was limited (21).

Despite promising and consistent evidence suggesting that use of glucosamine and chondroitin may be associated with a reduced risk of colorectal cancer, studies have not evaluated how use of the supplements relates to risk of adenomas and serrated polyps, colorectal cancer precursor lesions. Therefore, using three large prospective U.S. cohorts, we conducted the first study to evaluate the association of glucosamine and chondroitin with colorectal adenoma, with a particular focus on the high-risk adenomas most likely to develop into colorectal cancer. We additionally examined associations by

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Cancer Epidemiol Biomarkers Prev 2020;29:2693–701

doi: 10.1158/1055-9965.EPI-20-0805

consistency of use over time, and also using an updated exposure (most recent use). We also conducted secondary analyses examining associations between glucosamine and chondroitin use and any conventional adenoma, regardless of whether defined as high- or low-risk, as well as serrated polyps. We further explored whether associations pertaining to high-risk adenoma varied by subgroup and anatomic subsite.

Materials and Methods

Study population

Three ongoing prospective US cohorts were used for this study: (i) the Nurses' Health Study (NHS) was established in 1976 when 121,701 female registered nurses ages 30 to 55 years were enrolled, (ii) the Health Professionals Follow-up Study (HPFS) initiated in 1986 with 51,529 U.S. male health professionals ages 40 to 75 years, and (iii) the NHS2 initiated in 1989 with 116,671 female registered nurses ages 25 to 42 years. Participants were asked to complete questionnaires on demographic, lifestyle, and medical information at enrollment and every 2 years thereafter. Dietary information was assessed using a semiquantitative food frequency questionnaire (FFQ) every 4 years. The follow-up response rate exceeded 90%. For this study, we included participants who completed the 2002 questionnaire, when use of glucosamine and chondroitin was first assessed, and who had at least one lower gastrointestinal endoscopy (i.e., colonoscopy/sigmoidoscopy) over the follow-up period. We then excluded participants who reported a history of adenoma or any cancer (except nonmelanoma skin cancer) at baseline, familial polyposis, or inflammatory conditions including rheumatoid arthritis, ulcerative colitis, and Crohn's disease. The final sample included 17,553 women from NHS, 15,891 women from NHS2, and 9,719 men from HPFS. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health and those of participating registries, as required.

Glucosamine and chondroitin assessment

Use of glucosamine and chondroitin supplements was first assessed in the 2002 questionnaire and was assessed again in 2006. Participants were asked about use of specific supplements and if "there are other supplements (taken) on a regular basis." A list of supplements was provided, including glucosamine and chondroitin, from which participants could indicate regular use. From this information, participants were classified in terms of regular glucosamine use (yes vs. no). As chondroitin is rarely taken in the absence of glucosamine, we did not evaluate chondroitin and instead evaluated "glucosamine + chondroitin," representing use of both. As use of these supplements was assessed in both 2002 and 2006, we also conducted a secondary analysis of "consistent use" in which we compared consistent use (as reported in 2002 and 2006) and inconsistent use (use reported in 2002 or 2006, but not both) with nonuse (no use reported). In addition, we also conducted analysis of "updated exposure," which was defined as the most recently reported use of glucosamine and chondroitin prior to endoscopy.

Covariate assessment

From the biennial questionnaires, we collected detailed information on lifestyle and medical history such as height, weight, physical activity, smoking, family history of disease, medication use, and endoscopy. Validated FFQ was administered every 4 years to assess dietary factors (22–24) and overall diet quality was assessed by calculating the Alternate Healthy Eating Index (AHEI)-2010 score (25).

Colorectal adenoma assessment

Every 2 years, participants completed a biennial questionnaire, which includes information on screening and the detection of polyps in the past 2 years. Adenomas were assessed from 2002 to 2012 (as recorded in the 2004, 2006, 2008, 2010, and 2012 questionnaires). Cases and controls were defined within each 2-year period. All newly diagnosed adenomas were considered cases, and controls were comprised of all screened individuals who were found to be free of adenoma and colorectal cancer (26–28). Persons reporting a polyp were then asked for permission to obtain medical records and pathology reports. Medical records were obtained for over 90% of all reported polyps, from which investigators abstracted detailed information on polyp size, histology, and anatomic location. This information was used to identify high-risk adenoma, defined by large size (1+ cm in diameter), advanced histology (villous or tubulovillous histology or the presence of high-grade dysplasia), or multiplicity (detection of 3+ adenomas; ref. 26). If more than one adenoma was detected, cases were classified according to the largest size and most advanced histology. Although high-risk adenomas were the primary outcome of interest, we also examined the association for any adenoma (conventional adenoma, including both high-risk and low-risk conventional adenomas) and serrated polyps (defined in this study as hyperplastic polyps and mix/serrated adenomas), as well as by anatomic subsite (proximal, distal, or rectal). Of the 43,163 persons screened between 2002 and 2012, 5,715 conventional adenomas were detected, 2,016 of which were high-risk. A total of 4,953 serrated polyps were detected.

Statistical analysis

As noted previously, analyses were limited to those receiving at least one colonoscopy/sigmoidoscopy between baseline and the end of study. To account for the possibility that a person may have undergone multiple endoscopies over the study period, an Andersen–Gill structure was used with a new record created for each cycle that a participant reported an endoscopy (26–28). Once a participant was diagnosed with adenoma, the participant was censored in all subsequent cycles. Logistic regression was used to calculate an odds ratio and 95% confidence interval (CI) estimating the association between use of glucosamine and chondroitin and adenoma risk, accounting for clustered data.

Primary exposure was defined by the exposure at baseline (2002) reported prior to endoscopy and two separate models were run corresponding to each exposure of interest: any glucosamine and combined glucosamine + chondroitin. In minimally adjusted models of each sex-specific cohort, we adjusted for age, time period of endoscopy, number of endoscopies, time (in years) since the most recent endoscopy, and reason for the current endoscopy. In multivariable-adjusted models, we further adjusted for height, body mass index (BMI), physical activity, family history of colorectal cancer, history of diabetes, pack-years of smoking, alcohol intake, regular use of aspirin, regular use of NSAID, non-yogurt dairy intake, total calorie, folate, fiber, red and processed meat intake, calcium intake, vitamin D intake, and AHEI-2010 score. We ran these models for our primary outcome, high-risk adenoma, as well as for secondary outcomes: any conventional adenoma and serrated polyps. For serrated polyps, we conducted a sensitivity analysis restricting to high-risk serrated polyps [defined in this study as large (1+ cm in diameter) proximal serrated polyps]. All analyses were conducted separately within each sex-specific cohort and then effect estimates were pooled using a random-effects meta-analysis after testing for heterogeneity across cohorts. In addition to pooling the three cohorts, we separately pooled the NHS and HPFS because of similar age structure.

Table 1. Age-adjusted characteristics of participants at study baseline (2002) by combined use of glucosamine and chondroitin in the NHS, NHS2, and HPFS.

	NHS		NHS2		HPFS	
	Glucosamine + Chondroitin No use (n = 13,775)	**Glucosamine + Chondroitin Use (n = 2,921)**	**Glucosamine + Chondroitin No use (n = 12,795)**	**Glucosamine + Chondroitin Use (n = 1,526)**	**Glucosamine + Chondroitin No use (n = 7,127)**	**Glucosamine + Chondroitin Use (n = 1,393)**
Age (years)	67.1 (6.7)	67.3 (6.5)	50.9 (3.8)	52.0 (3.3)	66.9 (8.1)	66.8 (7.7)
Height (cm)	163.8 (6.2)	164.6 (6.1)	164.8 (6.6)	165.5 (6.5)	178.5 (6.7)	178.9 (6.4)
Body mass index (kg/m^2)	25.4 (4.3)	25.9 (4.5)	25.6 (5.2)	26.6 (5.7)	25.7 (3.2)	25.8 (3.0)
Family history of colorectal cancer (%)	17.9	16.7	13.7	11.5	12	10.5
History of diabetes (%)	8.7	7	3.9	4.1	8	6.2
Number of previous endoscopies	2.7 (1.7)	2.9 (1.7)	1.8 (1.1)	1.9 (1.2)	3.2 (1.9)	3.4 (2.0)
The most recent endoscopy (years)	3.9 (3.1)	3.8 (3.0)	3.4 (2.6)	3.4 (2.6)	4.1 (3.3)	4.0 (3.3)
Reasons for endoscopy run						
Screening (%)	72.2	73.3	69.9	71.5	78.0	82.5
Symptoms (%)	22.8	22.1	27.3	25.6	13.1	12
Missing (%)	5.0	4.6	2.9	2.9	9.0	5.4
Postmenopausal hormone use						
Premenopausal (%)	0.8	0.6	51.7	49.9	—	—
Postmenopausal never use (%)	19.0	14.1	13.3	12.1	—	—
Postmenopausal current use (%)	41.3	47.8	19.5	21.5	—	—
Postmenopausal past use (%)	39.0	37.5	15.6	16.5	—	—
Regular aspirin use (%)	36.9	39.9	13.4	17.6	59.5	62.8
Regular non-aspirin NSAID use (%)	24.6	30.2	33.5	45.2	22.8	32.9
Current use of multivitamin (%)	68.9	81.5	64.6	81.9	65.5	81
Alcohol intake (g/day)	5.9 (8.3)	6.0 (8.1)	4.2 (6.5)	4.5 (6.7)	11.2 (12.6)	11.3 (12.1)
Ever smokers (%)	52.8	53.6	34.3	38.4	46.4	50.2
Pack-years among ever smokers	21.3 (19.7)	18.6 (17.6)	13.8 (11.2)	13.6 (10.6)	22.2 (17.5)	20.0 (16.3)
Physical activity (MET-hours/week)	17.9 (16.1)	19.9 (18.8)	20.1 (19.5)	22.3 (23.0)	31.1 (22.4)	37.4 (25.3)
Total calorie intake (kcal/day)	1,714 (399)	1,742 (395)	1,801 (454)	1,832 (448)	1,982 (514)	2,003 (494)
Total calcium intake (mg/day)	1,087 (340)	1,218 (341)	1,227 (411)	1,405 (423)	969 (325)	1,104 (387)
Total Vitamin D intake (IU/day)	388 (175)	458 (184)	422 (201)	520 (204)	445 (215)	543 (247)
Total folate intake (μg/day)	492 (163)	559 (173)	571 (200)	661 (196)	611 (219)	718 (250)
Red and processed meat intake (servings/week)	5.5 (2.6)	5.4 (2.6)	6.1 (3.5)	5.8 (3.5)	5.9 (3.8)	5.6 (3.7)
Dietary fiber intake (g/day)	18.6 (4.3)	19.2 (4.3)	19.7 (4.9)	20.5 (4.8)	22.9 (6.0)	24.0 (6.0)
AHEI-2010	52.9 (9.0)	54.6 (9.2)	52.6 (9.8)	54.3 (9.9)	55.5 (9.9)	57.6 (10.1)

Note: Values are means (SD) for continuous variables, are percentages for categorical variables, and are standardized to the age distribution of the study population (except for age variable). Values of polytomous variables may not sum to 100% due to rounding.

As secondary analyses, we examined the association of consistent use of glucosamine + chondroitin (as determined by use in 2002 and 2006). For this analysis, only persons who received colonoscopies after the 2006 questionnaire were included. We also used an updated exposure which was defined as the exposure most recently reported prior to endoscopy.

To address concerns about potential residual confounding among aspirin/non-aspirin NSAID users, for our primary outcome of high-risk adenoma, we also conducted analyses stratified by ever use of NSAIDs, given that there was little opportunity for residual confounding by NSAID use among persons reporting no history of regular aspirin/non-aspirin NSAID use. Moreover, we further conducted stratified analyses by potential effect modifiers such as BMI, family history of colorectal cancer, smoking, physical activity, and age and then tested for heterogeneity across strata. Finally, we also evaluated the association by anatomical subsite (i.e., proximal, distal, and rectal).

All statistical analyses were performed using SAS version 9.4 (SAS Institute); all tests were two-sided and a P value of <0.05 was considered statistically significant.

Results

Table 1 shows baseline characteristics of participants by combined use of glucosamine and chondroitin in three cohorts. The mean ages of participants were 67 years for NHS, 68 years for HPFS, and 51 years for NHS2. Regardless of the supplement use, participants had similar number of previous endoscopies, time since the most recent endoscopy, and reasons for endoscopy. They also had similar age, BMI, and family history of colorectal cancer. However, participants with combined use of glucosamine and chondroitin had higher physical activity, aspirin/NSAID use, calcium intake, vitamin D intake, and folate intake, compared with nonsupplement users.

Use of glucosamine and chondroitin was associated with a 26% lower risk of high-risk adenoma among older adults in the pooled multivariable-adjusted analyses of NHS and HPFS (OR = 0.74; 95% CI, 0.60–0.90; $P_{heterogeneity} = 0.23$; **Table 2**; Supplementary Table S1). We observed comparable results when we examined the association of consistent use of the supplements or when using an updated exposure. However, we did not find an inverse association of glucosamine and chondroitin use with high-risk adenoma in younger women (NHS2; OR = 1.09; 95% CI, 0.82–1.45), nor did this association hold when pooled across all three cohorts (OR = 0.83; 95% CI, 0.63–1.10; $P_{heterogeneity} = 0.03$).

Use of any glucosamine or glucosamine + chondroitin at baseline was marginally significantly associated with any conventional adenoma in the two cohorts (**Table 3**; Supplementary Table S1). In the pooled age and screening-adjusted analysis of the NHS and HPFS, participants with combined glucosamine and chondroitin use had an 11% lower risk of conventional adenoma (OR = 0.89; 95% CI, 0.81–0.98; $P_{heterogeneity} = 0.80$), compared with nonsupplement users. When

Table 2. Associations of glucosamine and chondroitin with high-risk adenoma in the NHS, NHS2, and HPFS.

	High-risk adenoma				
OR (95% CI)	**NHS**	**HPFS**	**NHS2**	**NHS&HPFS**	**NHS&HPFS&NHS2**
Baseline exposure					
Any glucosamine					
No. of cases (yes/no)[a]	145/653	106/535	72/544		
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes-age adjusted[b]	0.81 (0.68–0.98)	0.78 (0.63–0.97)	0.90 (0.70–1.15)	0.80 (0.70–0.92)	0.82 (0.73–0.93)
Yes-MV[c]	0.79 (0.65–0.97)	0.87 (0.69–1.08)	1.02 (0.79–1.32)	0.82 (0.71–0.96)	0.87 (0.76–1.00)
Glucosamine + chondroitin					
No. of cases (yes/no)[a]	99/699	77/564	56/560		
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes-age adjusted[b]	0.71 (0.58–0.88)	0.74 (0.58–0.95)	0.96 (0.73–1.27)	0.73 (0.62–0.85)	0.79 (0.66–0.93)
Yes-MV[c]	0.67 (0.53–0.84)	0.82 (0.64–1.06)	1.09 (0.82–1.45)	0.74 (0.60–0.90)	0.83 (0.63–1.10)
Consistent use[d]					
Glucosamine + chondroitin					
No. of cases (yes/no)[a]	107/702	69/601	49/583		
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes-age adjusted[b]	0.82 (0.66–1.00)	0.76 (0.59–0.98)	1.06 (0.79–1.43)	0.79 (0.67–0.93)	0.85 (0.71–1.02)
Yes-MV[c]	0.82 (0.66–1.02)	0.82 (0.62–1.07)	1.17 (0.87–1.58)	0.82 (0.69–0.97)	0.91 (0.73–1.13)
Updated exposure[e]					
Glucosamine + chondroitin					
No. of cases (yes/no)[a]	119/679	100/549	60/553		
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes-age adjusted[b]	0.78 (0.64–0.95)	0.89 (0.72–1.11)	0.91 (0.69–1.19)	0.83 (0.72–0.96)	0.85 (0.74–0.96)
Yes-MV[c]	0.74 (0.60–0.91)	0.98 (0.78–1.23)	1.02 (0.78–1.35)	0.85 (0.64–1.12)	0.89 (0.72–1.10)

Abbreviation: MV, multivariable adjusted.

[a]Number of cases for glucosamine/chondroitin user (yes) and nonuser (no).

[b]Adjusted for age, time period of endoscopy, number of reported endoscopies, time since most recent endoscopy, and reason for current endoscopy.

[c]Additionally adjusted for height (continuous), body mass index (in quintiles), physical activity in metabolic equivalent tasks (in quintiles), family history of colorectal cancer (yes/no), history of diabetes (yes/no), pack-years of smoking (never, 1–4.9, 5–19.9, 20–39.9, 40+ pack-years), alcohol intake (<5, 5–9.9, 10–14.9, 15–29.9, 30+ g/day), regular use of aspirin (yes/no), NSAIDs (yes/no), non-yogurt dairy intake (in quintiles), total calorie (in quintiles), folate (in quintiles), fiber (in quintiles), red and processed meat intake (in quintiles), calcium intake (in quintiles), vitamin D intake (in quintiles), and AHEI-2010 (in quintiles).

[d]Defined as individuals who reported glucosamine and chondroitin use in 2002 and 2006.

[e]Defined as the most recently reported use of glucosamine and chondroitin prior to endoscopy.

Table 3. Associations of glucosamine and chondroitin with conventional adenoma in the NHS, NHS2, and HPFS.

	Conventional adenoma				
OR (95% CI)	**NHS**	**HPFS**	**NHS2**	**NHS&HPFS**	**NHS&HPFS&NHS2**
Baseline exposure					
Any glucosamine					
No. of cases (yes/no)[a]	428/1,613	284/1,224	292/1,959		
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes-age adjusted[b]	0.96 (0.86–1.07)	0.90 (0.79–1.03)	1.00 (0.88–1.14)	0.94 (0.86–1.02)	0.96 (0.89–1.03)
Yes-MV[c]	0.95 (0.85–1.07)	0.95 (0.82–1.09)	1.04 (0.91–1.18)	0.95 (0.87–1.04)	0.98 (0.91–1.05)
Glucosamine + chondroitin					
No. of cases (yes/no)[a]	309/1,732	218/1,290	210/2,041		
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes-age adjusted[b]	0.88 (0.78–1.00)	0.90 (0.78–1.05)	0.98 (0.85–1.14)	0.89 (0.81–0.98)	0.92 (0.85–0.99)
Yes-MV[c]	0.86 (0.75–0.98)	0.95 (0.81–1.11)	1.00 (0.86–1.17)	0.90 (0.81–0.99)	0.93 (0.85–1.02)
Consistent use[d]					
Glucosamine + chondroitin					
No. of cases (yes/no)[a]	345/1,726	205/1,350	205/2,105		
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes-age adjusted[b]	1.04 (0.92–1.17)	0.96 (0.82–1.12)	1.21 (1.05–1.41)	1.01 (0.92–1.11)	1.07 (0.94–1.21)
Yes-MV[c]	1.04 (0.92–1.18)	0.99 (0.84–1.16)	1.24 (1.07–1.45)	1.02 (0.92–1.13)	1.08 (0.95–1.23)
Updated exposure[e]					
Glucosamine + chondroitin					
No. of cases (yes/no)[a]	353/1,688	246/1,260	255/1,983		
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes-age adjusted[b]	0.90 (0.80–1.01)	0.93 (0.81–1.08)	1.06 (0.93–1.22)	0.91 (0.83–1.00)	0.96 (0.87–1.06)
Yes-MV[c]	0.88 (0.78–1.00)	0.97 (0.84–1.13)	1.10 (0.96–1.26)	0.92 (0.84–1.01)	0.98 (0.86–1.11)

Abbreviation: MV, multivariable adjusted.

[a]Number of cases for glucosamine/chondroitin user (yes) and nonuser (no).

[b]Adjusted for age, time period of endoscopy, number of reported endoscopies, time since most recent endoscopy, and reason for current endoscopy.

[c]Additionally adjusted for height (continuous), body mass index (in quintiles), physical activity in metabolic equivalent tasks (in quintiles), family history of colorectal cancer (yes/no), history of diabetes (yes/no), pack-years of smoking (never, 1–4.9, 5–19.9, 20–39.9, 40+ pack-years), alcohol intake (<5, 5–9.9, 10–14.9, 15–29.9, 30+ g/day), regular use of aspirin (yes/no), NSAIDs (yes/no), non-yogurt dairy intake (in quintiles), total calorie (in quintiles), folate (in quintiles), fiber (in quintiles), red and processed meat intake (in quintiles), calcium intake (in quintiles), vitamin D intake (in quintiles), and AHEI-2010 (in quintiles).

[d]Defined as individuals who reported glucosamine and chondroitin use in 2002 and 2006.

[e]Defined as the most recently reported use of glucosamine and chondroitin prior to endoscopy.

further adjusted for potential confounders, the association was slightly attenuated (OR = 0.90; 95% CI, 0.81–0.99; $P_{heterogeneity}$ = 0.36). We found slightly attenuated associations when we pooled all three cohorts. Moreover, we found similar associations when we analyzed using the updated exposure, instead of baseline exposure. However, when we examined the consistent use of glucosamine and chondroitin with conventional adenoma, we found no association overall (OR = 1.02; 95% CI, 0.92–1.13; $P_{heterogeneity}$ = 0.63) and a significant positive association in younger women (NHS2; OR = 1.24; 95% CI, 1.07–1.45).

We further examined the association of glucosamine and chondroitin use with serrated polyps (**Table 4**; Supplementary Table S1). Use of glucosamine and chondroitin at baseline was not associated with serrated polyps but consistent use of both supplements was associated with a 12% to 13% higher risk of serrated polyps in the pooled multivariable-adjusted analyses. When sensitivity analyses were conducted restricted to high-risk serrated polyps, the overall results did not materially change.

In stratified analyses of glucosamine and chondroitin use with high-risk adenoma, we found no statistically significant interactions by BMI, family history of colorectal cancer, smoking status, physical activity, aspirin use, NSAID use, or age ($P_{interaction}$ > 0.05; **Table 5**). However, we consistently observed lower risk of high-risk adenoma regardless of the subgroups. Finally, when we examined the associations by location of high-risk adenoma, the associations did not differ by anatomic subsites (proximal, distal, or rectal) in three cohorts (Supplementary Table S2).

Discussion

In three large U.S. cohorts, use of glucosamine and chondroitin was associated with a lower risk of high-risk and overall conventional adenoma in older women (NHS) and men (HPFS), whereas we found no inverse association among younger women (NHS2). In contrast, glucosamine and chondroitin use was not associated with risk of serrated polyps.

To our knowledge, this is the first study to evaluate the role of glucosamine and chondroitin use on colorectal adenoma risk. However, several studies have examined the association of these commonly used specialty supplements with colorectal cancer risk. From an exploratory analysis of various specialty supplements in the VITAL study, use of glucosamine and chondroitin was first shown to be significantly associated with reduced risk of colorectal cancer (17). These findings were then further explored in the same cohort with additional follow-up period (19) and three other cohorts including the NHS/HPFS (20), Cancer Prevention Study-II (CPS-II) Nutrition Cohort (18), and MCC-Spain Study (21). These studies consistently replicated the findings from the VITAL study showing that use of glucosamine alone or combined glucosamine + chondroitin was associated with approximately 12% to 25% decreased risk of colorectal

Table 4. Associations of glucosamine and chondroitin with serrated polyps in the NHS, NHS2, and HPFS.

	Serrated polyps				
OR (95% CI)	**NHS**	**HPFS**	**NHS2**	**NHS&HPFS**	**NHS&HPFS&NHS2**
Baseline exposure					
Any glucosamine					
No. of cases (yes/no)[a]	350/1,366	188/735	301/2,066		
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes-age adjusted[b]	0.93 (0.83–1.05)	1.00 (0.84–1.17)	1.00 (0.88–1.13)	0.95 (0.86–1.05)	0.97 (0.90–1.05)
Yes-MV[c]	0.93 (0.82–1.06)	0.99 (0.83–1.18)	0.99 (0.87–1.13)	0.95 (0.86–1.05)	0.97 (0.89–1.05)
Glucosamine + chondroitin					
No. of cases (yes/no)[a]	260/1,456	157/766	222/2,145		
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes-age adjusted[b]	0.89 (0.78–1.02)	1.10 (0.92–1.31)	1.00 (0.87–1.16)	0.98 (0.80–1.21)	0.98 (0.87–1.11)
Yes-MV[c]	0.88 (0.76–1.01)	1.10 (0.91–1.33)	0.99 (0.85–1.14)	0.97 (0.78–1.22)	0.97 (0.86–1.10)
Consistent use[d]					
Glucosamine + chondroitin					
No. of cases (yes/no)[a]	297/1,443	156/811	197/2,245		
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes-age adjusted[b]	1.07 (0.94–1.22)	1.23 (1.03–1.47)	1.11 (0.95–1.29)	1.13 (0.99–1.29)	1.12 (1.03–1.22)
Yes-MV[c]	1.09 (0.95–1.24)	1.22 (1.01–1.47)	1.10 (0.95–1.29)	1.13 (1.01–1.26)	1.12 (1.03–1.23)
Updated exposure[e]					
Glucosamine + chondroitin					
No. of cases (yes/no)[a]	304/1,413	178/756	255/2,095		
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes-age adjusted[b]	0.95 (0.83–1.08)	1.14 (0.96–1.34)	1.04 (0.91–1.19)	1.03 (0.86–1.23)	1.03 (0.93–1.13)
Yes-MV[c]	0.94 (0.83–1.08)	1.13 (0.95–1.34)	1.03 (0.90–1.18)	1.02 (0.86–1.22)	1.02 (0.93–1.12)

Abbreviation: MV, multivariable adjusted.

[a]Number of cases for glucosamine/chondroitin user (yes) and nonuser (no).

[b]Adjusted for age, time period of endoscopy, number of reported endoscopies, time since most recent endoscopy, and reason for current endoscopy.

[c]Additionally adjusted for height (continuous), body mass index (in quintiles), physical activity in metabolic equivalent tasks (in quintiles), family history of colorectal cancer (yes/no), history of diabetes (yes/no), pack-years of smoking (never, 1–4.9, 5–19.9, 20–39.9, 40+ pack-years), alcohol intake (<5, 5–9.9, 10–14.9, 15–29.9, 30+ g/day), regular use of aspirin (yes/no), NSAIDs (yes/no), non-yogurt dairy intake (in quintiles), total calorie (in quintiles), folate (in quintiles), fiber (in quintiles), red and processed meat intake (in quintiles), calcium intake (in quintiles), vitamin D intake (in quintiles), and AHEI-2010 (in quintiles).

[d]Defined as individuals who reported glucosamine and chondroitin use in 2002 and 2006.

[e]Defined as the most recently reported use of glucosamine and chondroitin prior to endoscopy.

cancer. When restricted to never-screened individuals to reduce any residual confounding due to heterogeneity in screening practices among the ever-screened, use of glucosamine alone or combined glucosamine + chondroitin showed substantially stronger inverse associations with colorectal cancer risk among never-screened individuals in the CPS-II (HR = 0.80) and the NHS/HPFS (HR = 0.58).

We found an inverse association of glucosamine and chondroitin use with high-risk adenoma, but the association was weaker for any conventional adenoma, for which low-risk adenomas predominate. Colorectal cancers develop over a period no less than 10 years (29) and most of them develop through an adenoma intermediate (30, 31). Our study suggests that glucosamine and chondroitin may act early in colorectal carcinogenesis. However, we found a marginal inverse association for overall conventional adenoma and no association for serrated polyps. This finding provides some evidence that glucosamine and chondroitin may primarily affect "high-risk" adenoma characterized by large size, advanced histology, or multiplicity, which are most likely to progress to colorectal cancer (32). It is also worth noting that most identified risk factors are stronger for high-risk adenoma (33). Furthermore, compared with inconsistent users of glucosamine/chondroitin, consistent users had lower risk of high-risk adenoma but not overall conventional adenoma. These suggest that longer duration of glucosamine/chondroitin use may play a role on the prevention of high-risk adenoma, although we had limited information to capture long-term use (duration) of glucosamine/chondroitin. More studies are needed to examine the potential chemopreventive effect of glucosamine and chondroitin—accounting for duration, dose, and timing—on colorectal adenoma, particularly high-risk adenoma, to confirm the observed findings from the observational studies.

It is well documented that inflammation plays an important role in the colorectal cancer development (2–7). Growing evidence from *in vitro* animal and human studies suggests that glucosamine and chondroitin may reduce risk of colorectal cancer through an anti-inflammatory mechanism. *In vitro* studies showed that glucosamine and chondroitin reduce inflammation by inhibiting NF-κB, a transcription factor central to the inflammatory cascade, from translocating to the nucleus (34–36). NF-κB lies upstream of many inflammatory factors (e.g., prostaglandin E_2, cyclooxygenase-2, TNFα, IL6) that promote cell growth and proliferation. Animal studies also showed corroborating evidence that glucosamine and chondroitin reduce the inflammatory markers downstream of NF-κB (37–42) and have an anti-inflammatory effect in the colon (43–45). Moreover, several human studies (14, 46–48), including two small RCT trials (14, 48), provided further evidence that glucosamine and chondroitin might have anti-inflammatory properties.

When we conducted stratified analyses, the observed inverse association of glucosamine and chondroitin with high-risk adenoma did not significantly differ by concurrent use of aspirin or other NSAIDs. This result minimizes the concern for residual confounding by NSAID use. Moreover, we found no significant interactions by other factors including BMI, family history of colorectal cancer, smoking, or

Table 5. Stratified analyses of the association of glucosamine and chondroitin with high-risk adenoma in the NHS, NHS2, and HPFS.[a]

	Glucosamine + chondroitin						
				NHS and HPFS		NHS and HPFS and NHS2	
OR (95% CI)	NHS	HPFS	NHS2	Pooled OR	$P_{interaction}$[b]	Pooled OR	$P_{interaction}$[b]
Body mass index							
Normal weight (<25 kg/m^2)	0.60 (0.42–0.86)	0.53 (0.33–0.86)	1.31 (0.87–1.97)	0.57 (0.43–0.76)	0.21	0.75 (0.43–1.30)	0.08
Overweight/obese (≥25 kg/m^2)	0.71 (0.53–0.96)	1.04 (0.77–1.41)	0.93 (0.62–1.39)	0.86 (0.60–1.24)		0.88 (0.69–1.11)	
Colorectal cancer family history							
No	0.66 (0.51–0.86)	0.83 (0.63–1.09)	1.06 (0.78–1.43)	0.74 (0.59–0.92)	0.64	0.83 (0.64–1.07)	0.83
Yes	0.68 (0.39–1.16)	0.69 (0.31–1.55)	1.28 (0.50–3.26)	0.68 (0.43–1.07)		0.77 (0.51–1.15)	
Ever smoking							
No	0.61 (0.43–0.87)	0.80 (0.54–1.19)	1.17 (0.82–1.67)	0.69 (0.53–0.90)	0.73	0.83 (0.57–1.22)	0.72
Yes	0.71 (0.53–0.96)	0.90 (0.63–1.27)	0.97 (0.60–1.58)	0.79 (0.63–0.99)		0.82 (0.66–1.01)	
Physical activity							
Low (<15 MET-hours/week)	0.63 (0.45–0.88)	1.14 (0.67–1.93)	1.18 (0.80–1.74)	0.81 (0.46–1.45)	0.11	0.92 (0.59–1.43)	0.29
High (≥15 MET-hours/week)	0.69 (0.50–0.96)	0.74 (0.55–0.99)	1.01 (0.66–1.54)	0.72 (0.58–0.89)		0.77 (0.64–0.94)	
Aspirin use							
No	0.66 (0.49–0.90)	0.80 (0.54–1.21)	0.94 (0.68–1.30)	0.71 (0.55–0.91)	0.97	0.79 (0.63–0.98)	0.97
Yes	0.68 (0.48–0.96)	0.83 (0.60–1.15)	NA	0.76 (0.60–0.96)		NA	
NSAID use (no aspirin)							
No	0.69 (0.53–0.90)	0.94 (0.70–1.26)	1.03 (0.70–1.52)	0.80 (0.59–1.07)	0.37	0.85 (0.67–1.09)	0.31
Yes	0.61 (0.38–0.98)	0.57 (0.34–0.95)	1.15 (0.75–1.78)	0.59 (0.42–0.84)		0.75 (0.48–1.18)	
Age group							
<65 years (NHS/HPFS)/ <50 years (NHS2)	0.55 (0.33–0.92)	0.80 (0.52–1.23)	1.06 (0.54–2.07)	0.68 (0.48–0.98)	0.15	NA	NA
≥65 years (NHS/HPFS)/ ≥50 years (NHS2)	0.70 (0.54–0.90)	0.85 (0.62–1.17)	1.10 (0.80–1.51)	0.75 (0.62–0.92)		NA	

Note: NA, not available due to insufficient power for aspirin analysis and use of different age cutpoints for age analysis.
[a]Multivariable relative risks were adjusted for age, time period of endoscopy, number of reported endoscopies, time since most recent endoscopy, reason for current endoscopy, height (continuous), body mass index (in quintiles), physical activity in metabolic equivalent tasks (in quintiles), family history of colorectal cancer (yes/no), history of diabetes (yes/no), pack-years of smoking (never, 1–4.9, 5–19.9, 20–39.9, 40+ pack-years), alcohol intake (<5, 5–9.9, 10–14.9, 15–29.9, 30+ g/day), regular use of aspirin (yes/no), NSAIDs (yes/no), non-yogurt dairy intake (in quintiles), total calorie (in quintiles), folate (in quintiles), fiber (in quintiles), red and processed meat intake (in quintiles), calcium intake (in quintiles), vitamin D intake (in quintiles), and AHEI-2010 (in quintiles).
[b]$P_{interaction}$ indicates whether the pooled association varies by a given stratifying factor.

physical activity. Our study shows that glucosamine and chondroitin may influence colorectal adenoma regardless of factors associated with inflammation. However, we had limited power to detect the differences in the associations by the subgroups; thus, additional studies with larger sample size are needed to better understand the interactive role of glucosamine/chondroitin and the aforementioned factors on inflammation and colorectal carcinogenesis.

Unlike the inverse association of glucosamine and chondroitin use with high-risk and overall conventional adenoma in older adults (NHS and HPFS), we did not find any meaningful associations for younger women (NHS2), except that we observed a marginal positive association with proximal high-risk adenoma. The mean ages at baseline were approximately 67 to 68 years for NHS/HPFS and 51 years for NHS2, and there was a significant heterogeneity across cohorts when NHS2 was further included for the pooled analysis. We also conducted analysis stratified by age, but the overlapping age range was narrow between NHS/HPFS and NHS2; thus, the age stratified analysis in NHS/HPFS was limited in its ability to provide further insights to explain the null results for NHS2. Previous analyses of glucosamine/chondroitin use and colorectal cancer risk have been conducted mostly in older adults, with little known about associations in younger adults. The observed null or some positive findings may be due to chance or reflect true differences in the associations by age. Of note, almost half of the endoscopies in NHS2 were done in those under age 50, which is prior to the standard age of screening. It is unclear if some selection bias affected the results in either the young or older groups, although since the majority of endoscopies in the older group were mostly done for screening, it is less apparent that selection bias was operative in this group.

There are several limitations in this study. First, due to lack of data, we were not able to evaluate whether the association differs by frequency and duration of use. Moreover, given small numbers and patterns of use, we were not able to examine associations for glucosamine alone and chondroitin alone with adenoma risk. However, the lack of data on associations pertaining to use of chondroitin alone is a limitation for most studies because chondroitin is rarely used alone in the absence of glucosamine. Although we had detailed and updated information on potential confounders, we cannot rule out the possibility of unmeasured or residual confounding. Finally, our study included predominantly White health professionals which may limit the generalizability of our findings. However, inclusion of highly educated health professionals increases the accuracy of collected health data and consequently strengthens internal validity of the study.

In conclusion, we found that use of glucosamine and chondroitin was associated with a lower risk of high-risk and overall conventional adenoma in older adults. However, no inverse association was observed in younger adults, or for serrated polyps. Our findings provide first evidence that use of glucosamine and chondroitin may act in early colorectal carcinogenesis in older adults. Given their

favorable safety profile, glucosamine and chondroitin have the potential to be safely used for primary prevention in the population setting (12, 49). More studies are warranted to confirm our findings in diverse racial and ethnic populations.

Disclosure of Potential Conflicts of Interest

K. O'Connell reports grants from NIH R03 (R03 CA212983) during the conduct of the study. M. Du reports grants from NCI during the conduct of the study. K.D. Kantor reports grants from NCI (R03 CA212983 and P30 CA008748) during the conduct of the study. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

D.H. Lee: Conceptualization, investigation, writing–original draft, writing–review and editing. **C. Cao:** Conceptualization, formal analysis, investigation, writing–review and editing. **X. Zong:** Formal analysis, investigation, writing–review and editing. **X. Zhang:** Investigation, writing–review and editing. **K. O'Connell:** Investigation, writing–review and editing. **M. Song:** Investigation, writing–review and editing. **K. Wu:** Investigation, writing–review and editing. **M. Du:** Investigation, writing–review and editing. **Y. Cao:** Conceptualization, supervision, investigation, writing–review and editing. **E.L. Giovannucci:** Conceptualization, supervision, funding acquisition, investigation, writing–review and editing. **E.D. Kantor:** Conceptualization, supervision, funding acquisition, investigation, writing–review and editing.

Acknowledgments

The authors thank the participants and staff of the NHS and HPFS for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data. The Health Professionals Follow-up Study is supported by NIH U01 CA167552. The NHS was supported by NIH UM1 CA186107 and P01 CA87969. The NHS2 was supported by NIH U01 CA176726. This work was additionally supported by NIH grants: P30 CA008748 and R00 CA215314 to M. Song; R21 CA222940, R21 CA230873, and R03 CA197879 to K. Wu; and R03 CA212983 to E.D. Kantor. This work was also, in part, supported by Investigator Initiated Grants from the American Institute for Cancer Research (AICR) to K. Wu.

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Received May 24, 2020; revised August 17, 2020; accepted September 22, 2020; published first October 14, 2020.

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