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Use of glucosamine and chondroitin supplements and risk of colorectal cancer

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Abstract

Purpose—Glucosamine and chondroitin are non-vitamin, non-mineral supplements which have anti-inflammatory properties. These supplements are typically used for joint pain and osteoarthritis, and are commonly taken as either glucosamine alone or as glucosamine plus chondroitin. An exploratory analysis conducted within the VITamins And Lifestyle (VITAL) study observed any use of glucosamine and chondroitin to be associated with reduced risk of colorectal cancer (CRC) after 5 years of follow-up.

Methods—With two additional years of follow-up, we have studied these associations in greater depth, including associations by frequency/duration of use and by formulation, and have evaluated whether observed associations are modified by factors associated with inflammation. Participants include 75,137 western Washington residents aged 50–76 who completed the mailed VITAL questionnaire between 2000–2002. Use of glucosamine and chondroitin was ascertained by questions about supplement use during the 10-year period prior to baseline, and participants were followed for CRC through 2008 (n=557). Cox regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results—Persons reporting use of glucosamine+chondroitin on 4+ days/week for 3+ years had a non-statistically significant 45% lower CRC risk than non-users (HR: 0.55; 95% CI: 0.30–1.01; p-trend: 0.16). This association varied by body mass index (p-interaction: 0.006), with inverse association observed among the overweight/obese (p-trend: 0.02), but not among the underweight/normal-weight. Use of glucosamine alone was not significantly associated with CRC risk.

Conclusions—There is great need to identify safe and effective cancer preventive strategies, suggesting that glucosamine and chondroitin may merit further attention as a potential chemopreventive agent.

Keywords

chemoprevention; chondroitin; colorectal cancer; epidemiology; glucosamine

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INTRODUCTION

Glucosamine and chondroitin are non-vitamin, non-mineral specialty supplements commonly used for joint pain and osteoarthritis. These supplements are often but not always taken together in a single daily supplement, and are sometimes additionally coupled with methylsulfonylmethane (MSM). While the effectiveness of these supplements on joint pain and function is debated [1–5], glucosamine and chondroitin are among the most commonly used supplements in the United States: 7.4% of older adults report use of glucosamine-chondroitin, a prevalence of use comparable to acetaminophen [6].

Beyond the inconclusive randomized control trial evidence for an effect on joint function [3–5], results of human, animal, and laboratory studies suggest that glucosamine and chondroitin may have anti-inflammatory properties [7–13]. Given that chronic inflammation has been linked to the development of colorectal cancer (CRC) [14–19], there is substantial interest in assessing whether factors which reduce inflammation have potential utility in CRC prevention. To this end, an exploratory analysis of 11 supplements conducted within the VITamins And Lifestyle (VITAL) study observed that use of glucosamine and chondroitin supplements were associated with reduced risk of CRC after 5 years of follow-up [20].

With an additional 2 years of follow-up in the VITAL cohort, we have further investigated the associations between use of glucosamine and chondroitin supplements and CRC, with analyses designed to examine associations by formulation and by dose-response. We also assessed whether observed associations were modified by factors associated with inflammation and whether associations varied by cancer subsite and stage.

METHODS

Study Population

Study participants were drawn from the VITAL study, a prospective cohort of persons aged 50–76 years residing in the 13-county western Washington catchment area of the Surveillance, Epidemiology, and End Results (SEER) cancer registry [21]. Potential participants were identified by purchased commercial mailing list, and were mailed a 24-page questionnaire and reminder postcard between October 2000 and November 2002. Of the 364,418 persons included in mailings, 77,719 returned the questionnaire and met eligibility requirements. We excluded persons with a history of CRC as of baseline (n=971), as well as those for whom this information was missing (n=213). We also excluded persons with history of ulcerative colitis or Crohn's disease (n=1030), intestinal polyposis (n=273), or malabsorptive syndromes (n=42). Additional exclusion criteria included diagnosis with *in situ* CRC over follow-up (n=12), cancer noted on death certificate only with no diagnosis date available (n=1), and diagnosis with CRC of certain rare morphologies, including malignant carcinoid tumors and lymphomas (n=33). Persons were also excluded if missing information on use of glucosamine, chondroitin, and MSM supplements (n=60), leaving 75,137 persons for analyses. The above-listed exclusions are not mutually exclusive and persons may have been excluded for more than one reason.

Exposure

Use of glucosamine, chondroitin, and MSM supplements was ascertained by a series of questions about use of various supplements in the 10-year period prior to baseline, including years of use and average number of days/week of use. For all analyses, our reference group was defined as non-users of glucosamine, chondroitin, and MSM supplements so as to yield the most pure group for comparison.

We classified use of glucosamine into 3 categories: high use (4+ days/week for 3+ years), low use (<4 days/week or <3 years), or no use of glucosamine, chondroitin, or MSM. These categories were created *a priori* so that the highest level of exposure is defined by high frequency (4+days/week) and substantial duration (3+ years) of use. Given that approximately 72% of glucosamine users also report use of chondroitin or MSM, we created a second glucosamine variable in order to parse apart effects of these supplements and examine the effects of glucosamine alone. For this variable, users were defined as persons using glucosamine only (persons reporting chondroitin or MSM were excluded from these analyses).

We were unable to examine the association between chondroitin and CRC independently, as over 99% of chondroitin users in our study also reported use of glucosamine or MSM. We have therefore created a variable to capture joint glucosamine+chondroitin use, with high use defined by use of both glucosamine and chondroitin supplements on 4+ days/week for 3+ years. Persons were classified as low use if they reported use of glucosamine and chondroitin but did not meet the definition of high use for both supplements, while non-use was defined as non-use of glucosamine, chondroitin, and MSM. Persons reporting use of either glucosamine or chondroitin alone were excluded from these analyses.

MSM was defined as high use (4+ days/week for 3+ years), low use (<4 days/week or <3 years), or no use of glucosamine, chondroitin, or MSM. We were unable to create an "MSM alone" variable, as this less-commonly used supplement is rarely taken in the absence of glucosamine and/or chondroitin: 83% of MSM users also report use of glucosamine or chondroitin.

Potential confounders

Covariates included in multivariate analyses were selected *a priori* and include factors associated with CRC, as well as factors associated with glucosamine use, including: older age, female sex, increased levels of physical activity, never smoking, and history of osteoarthritis or joint pain [22]. Our multivariate analyses therefore include the following covariates: age (time-metric of analysis), sex, race/ethnicity (white, Hispanic, black, American Indian/Alaska Native, Asian or Pacific Islander, or other), educational status (high school graduate/GED or less, some college or technical school, or college graduate or above), body mass index (BMI)(kg/m^2; classified as normal weight[<25], overweight[25–<30], obese[30–<35], and severely obese[35+]), physical activity (no moderate/vigorous activity, sex-specific tertiles of MET-hours per week of moderate/vigorous physical activity), smoking history (never, quit 10+ years before baseline, quit <10 years before baseline, current), energy intake (quartiles), total calcium intake (quartiles of dietary +supplemental intake), alcohol consumption (none-<1 drink/mo, 1 drink/mo-<4 drinks/wk, >4 drinks/wk-<2 drinks/day, 2+ drinks/day), multivitamin use (never, past, current), dietary fiber intake (quartiles), fruit/vegetable intake excluding potatoes (quartiles), red/processed meat intake (quartiles), hormone replacement therapy (never, former, current), as well as aspirin use and non-aspirin NSAID use (none, low, high use; high use defined by use 4+ days/week for 4+ years). Analyses also included adjustment for family history of CRC among 1^{st} degree relatives (yes/no), history of sigmoidoscopy/colonoscopy in the 10 years prior to baseline (yes/no), and history of polyp excision (yes/no). We also adjusted for history of osteoarthritis or joint pain, as these conditions are the usual indications for use of glucosamine, chondroitin or MSM supplements.

BMI was determined by self-reported height and baseline weight. 1323 persons were missing baseline weight, but reported weight at age 45. For this group, we estimated baseline BMI by first calculating the average BMI change/year within sex-age-race group

among those with complete data. We then applied the group-specific average BMI change/year to the number of years elapsing since age 45.

Information on diet was ascertained by a food-frequency questionnaire (FFQ) adapted from the Women's Health Initiative [23] which captures frequency and serving size of 120 foods and beverages consumed over the year prior to baseline. Participants were excluded from nutrient calculations if they did not complete all pages of the FFQ, or if they reported abnormally high or low energy intake (men: <800 kcal/day or >5000 kcal/day; women: <600 kcal/day or >4000 kcal/day).

Outcome

Cases were identified by linkage to the western Washington SEER registry, which uses information from area hospitals, state death certificates, as well as offices of oncologists, radiologists, and pathologists to find cases. Between baseline and December 2008, 557 invasive cancers of the colon and rectum were diagnosed.

Statistical Analysis

Cox regression was used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for associations between supplement use and CRC risk, with exposures and covariates modeled using indicator variables. For exposures under study, we additionally present tests for trend, with corresponding p-values obtained by alternatively modeling the exposures as continuous categorical variables. Analyses were conducted using Stata (version 12, College Station, TX). Study participants provided informed consent and study procedures were approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Participants entered analysis at the time baseline questionnaire was received and were followed for an average of 6.7 years. Cases were followed until date of CRC diagnosis and non-cases were censored at whichever occurred earliest: date of death (6.7%), date of emigration out of the SEER catchment area (5.5%), date of requested removal from study (0.03%), or December 31st, 2008 (87.8%). Deaths occurring within the state of Washington were identified by linkage to the state death file, while emigrations out of area were identified by linkage to the National Change of Address System and by telephone calls and mailings.

We additionally tested for effect modification of the association between glucosamine +chondroitin use and CRC by factors associated with inflammation, including: sex, regular aspirin use in the 10-years prior to baseline (yes/no; regular use defined as use on 1+ days/week for 1+years), and BMI (<25, 25+). A single interaction term was used to test for interaction, with glucosamine+chondroitin modeled as a continuous-categorical variable. We also tested for differences in association across cancer site (colon vs. rectum) and stage (local vs. regional/distant). In determining the HRs associated with each particular subsite, cases of the subsite not under study were censored at date of diagnosis. For analyses of stage, we instead opted to exclude cases of the stage not under study, given concern that censoring of these cases would violate the assumption of non-informative censoring. Logistic regression limited to cases was used to determine the statistical significance of subsite-and stage-specific differences.

RESULTS

Persons in the overall cohort reported a mean age of 61.4 years at baseline. In our study population, glucosamine+chondroitin users were more likely to be older, female, and more highly educated than non-users (Table 1). As compared to non-users, glucosamine

+chondroitin users were less likely to smoke, were more physically active, and were more likely to report use of aspirin, non-aspirin NSAIDs, and multivitamins. Glucosamine +chondroitin users also consumed more vegetables and less red/processed meat than non-users, and were more likely to have a history of screening and history of arthritis or joint pain.

Persons reporting high use of glucosamine (4+ days/week for 3+ years in the 10 year period prior to baseline), with or without use of chondroitin or MSM (n=5,395), had a 29% lower risk of CRC as compared to persons reporting no use of glucosamine, chondroitin, or MSM in this time frame (HR: 0.71; 95% CI: 0.46–1.11; p-trend: 0.19) (Table 2). Use of glucosamine alone (n=1,229) was not associated with risk of CRC (HR: 0.86; 95% CI: 0.38–1.94 for high use; p-trend: 0.84). Persons reporting high use of glucosamine+chondroitin (n=3,481) had 45% lower risk of CRC than persons not using glucosamine, chondroitin, or MSM in the 10 years prior to baseline (HR: 0.55; 95% CI: 0.30–1.01), though the test for trend did not reach significance (p-trend: 0.16). High use of MSM, which is usually, but not always, taken as part of a glucosamine and chondroitin supplement, was associated with a 52% reduced risk of CRC as compared to no use of glucosamine, chondroitin, or MSM (HR: 0.48; 95% CI: 0.12–1.94; p-trend: 0.14).

We found no evidence for effect modification by sex (p-interaction: 0.19) or aspirin use (p-interaction: 0.19) (Table 3). However, we did observe that the association between glucosamine+chondroitin and CRC varied by BMI (p-interaction: 0.006), with no association observed among those of normal weight and an inverse association observed among the overweight/obese (p-trend: 0.02). Among the overweight/obese group, persons reporting high use of glucosamine+chondroitin experienced 72% lower risk of CRC than non-users of glucosamine, chondroitin, and MSM (HR: 0.28; 95% CI: 0.10–0.76). The association between glucosamine+chondroitin use and cancer risk did not vary by subsite (p-difference: 0.56) or stage (p-difference: 0.19) (Table 3). Furthermore, we observed that the association between use of glucosamine+chondroitin and CRC was strong in the first half of follow-up (HR high use vs no use: 0.28; 95% CI: 0.09–0.89; p-trend: 0.03), while no association was observed in the latter half of follow-up (HR: 0.85; 95% CI: 0.41–1.76; p-trend: 0.80) (Table 4). Also, to further rule out confounding by multivitamin use, we conducted a sensitivity analysis restricted to persons reporting no use of multivitamins at baseline. The association between glucosamine+chondroitin use and CRC did not change meaningfully (data not shown).

DISCUSSION

In this prospective cohort study, use of glucosamine with or without chondroitin for 4+ days/week for 3+years was associated with a non-significant 29% reduction in CRC risk (HR: 0.71; 95% CI: 0.46–1.11; p-trend: 0.19). The association with CRC was stronger for use of the combination glucosamine+chondroitin: those who used the combination for 4+ days/week for 3+ years had 45% lower risk of CRC as compared to non-users of glucosamine, chondroitin and MSM (HR: 0.55; 95% CI: 0.30–1.01) though the overall trend did not reach statistical significance (p-trend: 0.16). The association between glucosamine+chondroitin and CRC varied by BMI (p-interaction: 0.006), with the inverse association observed among the overweight/obese only. Use of glucosamine alone was not associated with CRC risk.

In the prior exploratory analysis conducted within the VITAL cohort, any use of glucosamine was associated with a 27% reduced risk of CRC (HR: 0.73; 95% CI: 0.54–0.98; p: 0.03) and any use of chondroitin in the 10-year period prior to baseline was associated with a 35% reduced risk of CRC (HR: 0.65; 95% CI: 0.45–0.93; p: 0.02) (20). With an additional two years of follow-up in our current study, we similarly observed a reduction in

CRC risk associated with use of these supplements, though results did not reach statistical significance. To better understand why results were weaker in this report, we conducted a sensitivity analysis in which we examined the association between glucosamine+chondroitin use and CRC risk separately within the first and second half of follow-up. A strong association was observed in the first half of follow-up, with no association in the latter half, suggesting that the observed differences reflect the increased length of follow-up rather than differences in exposure definition, covariate selection, or exclusion criteria between the analyses. Given the increasing popularity of glucosamine and chondroitin supplements over the last decade (24), we would expect that patterns of use changed over follow-up. If the etiologically relevant time frame extends into follow-up, these changes in exposure status would act to increase measurement error of exposure. Such measurement error would likely attenuate results toward the null as the length of time between exposure ascertainment and the end-of-follow-up increases, fitting with our observation of a weaker association in the latter half of follow-up. In our current study, we further explored associations between these supplements and CRC by formulation. Given that associations were strongest for glucosamine+chondroitin (p-trend: 0.16) and use of glucosamine alone was not associated with CRC risk (p-trend: 0.84), it seems possible that either chondroitin or the combination of glucosamine+chondroitin may be driving observed associations. However, such conclusions are tempered by the lack of statistical significance of our associations, and by the fact that we were unable to examine the association between chondroitin alone and CRC since chondroitin is rarely taken without glucosamine.

Beyond the prior VITAL study, no other studies have reported on the association between glucosamine and chondroitin supplements and CRC risk. However, results of our study may be compared to studies of aspirin, another anti-inflammatory which has been extensively studied in terms of CRC risk. A recent meta-analysis of randomized control trials (RCTs) has shown that aspirin use reduces risk of CRC by 24% (HR: 0.76, 95% CI: 0.60–0.96) [25], with the association strengthening when restricted to persons allocated to 5 or more years of use (HR: 0.68; 95% CI: 0.54–0.87) [25]. Research also suggests that frequency of use may be an important component of the association between aspirin and CRC. In both the Nurses' Health Study [26] and Health Professionals Follow-up Study [27], Chan and colleagues observed increasing frequency of aspirin use to be associated with decreased risk of CRC (p-trend: 0.007, 0.004, respectively). To this end, we have incorporated both duration (years) and frequency of use (days/week) into our supplement variables. In our study, we see that the trend for 'dose' is not significant for any of the supplements under study, with strongest associations observed among the high 'dose' users. It is possible that we did not observe a significant trend as a combination of high frequency and long duration of use may be needed to see effect. It is also possible that our power to detect significant association was limited by the small number of supplement users.

In addition to being associated with CRC risk, use of glucosamine and chondroitin supplements has been associated with reduced risk of lung cancer [20,28] and total mortality [22,29] in VITAL. In particular, Brasky et al. observed use of glucosamine (with or without chondroitin) on 4+days/week for 3+years to be associated with a 51% reduced risk of adenocarcinoma of the lung (HR: 0.49; 95% CI: 0.27–0.90) [28], a finding which aligns with randomized trial evidence showing that aspirin reduces risk of lung adenocarcinoma [30]. It should also be noted, however, that other studies conducted within VITAL have not observed an association between glucosamine/chondroitin use and bladder cancer [31], prostate cancer [32], breast cancer [33], or hematologic cancers [34].

In our study, we observed that the association between glucosamine+chondroitin use and CRC risk varied by BMI (p-interaction: 0.006), with significant inverse association observed among those who are overweight/obese (p-trend: 0.02), and no association observed among

the underweight/normal-weight. This interaction supports our hypothesis that these posited anti-inflammatory supplements may be most strongly associated with CRC risk among the group likely to have highest inflammation, (i.e., the overweight/obese) [35], though these sub-group analyses should be interpreted cautiously given the small number of cases within strata While this question has not been previously addressed in terms of glucosamine and chondroitin, studies have assessed whether BMI modifies the association between aspirin/NSAID use and CRC, and results have been inconsistent. A recent RCT reported that normal-weight persons and overweight persons given 325 mg aspirin/day experienced no reduction in risk of advanced adenoma as compared to persons receiving the placebo (RR: 1.23; 95% CI: 0.55–2.77; RR: 0.94; 95% CI: 0.54–1.64, respectively), while a RR of 0.44 (95% CI: 0.17–1.10) was reported among the obese [36]. However, another study conducted within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) suggested just the opposite: an inverse association was observed between NSAID use and risk of left-sided colon adenoma among women with BMI<25, while no association was observed among women of higher BMI [37].

If these supplements have the potential to reduce risk of CRC, it would likely be through reduction in inflammation. Laboratory research suggests that glucosamine and chondroitin may affect inflammation through the nuclear factor kappa B (NF-κB) pathway [10–12]. NF-κB is a transcription factor which lies upstream of many inflammatory processes and which has been implicated in various inflammation-related cancers [38]. Recent research conducted using a mouse epidermal cell line demonstrated that chondroitin sulfate inhibits NF-κB activity by preventing degradation of the NF-κB inhibitory subunit, IκB [11]. Glucosamine has been shown to similarly inhibit NF-κB activity in a dose-dependent manner [10]. In support of these findings, *in vitro* and animal studies suggest that glucosamine and chondroitin administration is associated with decreased levels of various inflammatory biomarkers associated with the NF-κB pathway, including IL-1β, IL-6, PGE_2, and TNF-α. [7–10,39]. *In vivo* research conducted in rats with chemically-induced colitis has further demonstrated that glucosamine reduces colonic inflammation and that both glucosamine and chondroitin have therapeutic effects, potentially reflecting the possible anti-inflammatory effects of these supplements [40,41].

Two studies suggest that these anti-inflammatory effects may extend to humans. Nakamura and colleagues measured serum PGE_2 in a group of 36 persons with osteoarthritis at baseline and after 3 months of glucosamine-chondroitin administration [9]. Study authors observed a significant decrease in serum PGE_2, and the post-intervention PGE_2 level among the osteoarthritic group was similar to the serum PGE_2 level among 25 age-matched healthy controls. This evidence, while limited, is corroborated by a large recent observational study conducted within the National Health And Nutrition Examination Survey (NHANES), a nationally-representative sample of nearly 10,000 adults, in which we observed that persons reporting regular current chondroitin use had 22% lower levels of circulating serum CRP than non-users (95% CI: 8%–33%), and current glucosamine users had 17% lower CRP than non-users (95% CI: 7%–26%) (13).

Our study may be limited by measurement error in supplement use, as supplement use was ascertained by self-report, and, as noted above, was limited to use before baseline. We were therefore unable to account for changes in exposure status after baseline. Furthermore, we do not have information on the dose used, preventing estimation of average daily dose. Another potential limitation of this study is residual confounding. This may be of particular concern when studying healthy behaviors, such as supplement use. To address this concern, we have adjusted for several potential confounding factors, including factors associated with health behaviors (i.e., history of sigmoidoscopy/colonoscopy, use of multivitamins, education, and smoking history, among others). We are also limited by small sample size

especially when conducting subgroup analyses, limiting our ability to detect subgroup-specific associations.

Our study also has several strengths. Since VITAL was designed to assess the association between supplement use and cancer, we have information on supplement use in the 10-year period prior to baseline, as well as detailed information on various potential confounding factors, including several health behaviors and conditions that are indications for supplement use. It should also be noted that we have shown good reliability and validity of supplement use as reported in the VITAL baseline questionnaire [42], though the reliability and validity of these specific supplements have not been examined. Furthermore, we expect nearly complete case ascertainment, as cases were identified by annual linkage to SEER.

In summary, our research provides limited support that use of glucosamine plus chondroitin may merit further attention as a potential chemopreventive agent, though a larger study would be needed to assess these associations with greater precision.. Since CRC is major cause of morbidity and mortality, it is important that we seek potential preventive strategies which are safe, effective, and easily implemented. Glucosamine and chondroitin supplements have been shown to be safe [4,43–45] and are already widely used [6], and it is therefore important that we seek to better understand the suggestive association between use of these supplements and CRC.

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Table 1

Distribution of Colorectal Cancer Risk Factors and Arthritis among Glucosamine and Chondroitin Non-Users and Users

	Glucosamine + Chondroitin Non-Users[a] (n=59,024) *n* (%)	Glucosamine + Chondroitin Users[b] (n=9,990) *n (%)*
Age at Baseline (yrs)		
50–<55	14,513 (24.6)	1,748 (17.5)
55–<60	13,617 (23.1)	2,107 (21.1)
60–<65	10,561 (17.9)	1,994 (20.0)
65–<70	9,406 (15.9)	1,886 (18.9)
70+	10,927 (18.5)	2,255 (22.6)
Sex		
Female	29,046 (49.2)	6,212 (62.2)
Male	29,978 (50.8)	3,778 (37.8)
Education		
High School Graduate	12,053 (20.8)	1,602 (16.3)
Some College or Tech	21,990 (37.9)	3,778 (38.4)
College Graduate or Higher	23,960 (41.3)	4,460 (45.3)
Smoking		
Never Smoker	27,573 (47.3)	4,956 (50.1)
Former Smoker (Quit 10+ Years Prior)	21,213 (36.4)	3,985 (40.2)
Former Smoker (Quit <10 Years Prior)	4,084 (7.00)	521 (5.26)
Current Smoker	5,462 (9.36)	440 (4.44)
Body Mass Index (m/kg^2)		
Normal Weight (<25)	19,604 (34.3)	3,327 (34.2)
Overweight (≥25–<30)	23,655 (41.4)	3,894 (40.1)
Obese (≥30–<35)	9,435 (16.5)	1,597 (16.4)
Severely Obese (≥35)	4,414 (7.73)	904 (9.30)
Physical Activity (MET-hrs per week mod/vig activity)[c]		
None	31,010 (53.3)	4,476 (45.4)
Tertile 1	9,339 (16.1)	1,634 (16.6)
Tertile 2	8,990 (15.5)	1,799 (18.2)
Tertile 3	8,846 (15.2)	1,954 (19.8)
Aspirin Use[d]		
Non-user	32,464 (56.7)	4,726 (48.3)
Low (<4 days per week or <4 years)	12,921 (22.6)	2,582 (26.4)
High (4+ days per week for 4+ years)	11,865 (20.7)	2,474 (25.3)
Non-Aspirin NSAID Use[e]		
Non-user	42,480 (73.6)	5,288 (53.8)
Low (<4 days per week or <4 years)	12,004 (20.8)	3,310 (33.7)
High (4+ days per week for 4+ years)	3,263 (5.65)	1,238 (12.6)
Multivitamin Use		

	Glucosamine + Chondroitin Non-Users[a] (n=59,024) *n* (%)	Glucosamine + Chondroitin Users[b] (n=9,990) *n (%)*
Never	23,337 (39.5)	1,644 (16.5)
Past Only	4,527 (7.67)	743 (7.44)
Current	31,151 (52.8)	7,603 (76.1)
Fruit/Vegetable Consumption (serv/day; excludes potatoes)		
Quartile 1: <2.0	14,373 (26.9)	1,516 (16.3)
Quartile 2: 2.0–<3.2	13,613 (25.5)	2,104 (22.6)
Quartile 3: 3.2–<4.8	13,046 (24.5)	2,528 (27.1)
Quartile 4: 4.8+	12,324 (23.1)	3,166 (34.0)
Red/Processed Meat Intake (oz/week)[f]		
Quartile 1: <9.11	12,762 (23.9)	2,625 (28.2)
Quartile 2: 9.11–<17.1	13,150 (24.7)	2,452 (26.3)
Quartile 3: 17.1–<28.3	13,414 (25.1)	2,348 (25.2)
Quartile 4: 28.3+	14,030 (26.3)	1,889 (20.3)
History of Sigmoidoscopy/Colonoscopy (last 10 yrs)		
No	26,390 (45.1)	3,755 (37.8)
Yes	32,112 (54.9)	6,170 (62.2)
Arthritis or Joint Pain		
Neither	34,066 (57.7)	2,668 (26.7)
Either Arthritis or Joint Pain	24,958 (42.3)	7,322 (73.3)

Abbreviations: MET (Metabolic Equivalent of Task); NSAID (Non-Steroidal Anti-Inflammatory Drug)

[a] Non-user group defined by no use of glucosamine, chondroitin, and methylsulfonylmethane (MSM) in the 10 years prior to baseline; MSM was incorporated in this definition of non-use, as MSM is often a component of joint supplements

[b] Glucosamine+chondroitin use defined by use of both glucosamine and chondroitin in the 10 years prior to baseline; persons reporting use of glucosamine, chondroitin, or MSM alone are omitted

[c] Tertiles of physical activity among those engaging in moderate/vigorous leisure time physical activity determined within sex; women (T1: <2.81; T2: 2.81–<9.47; T3: 9.47+); men (T1: <−4.34; T2: 4.34–<13.2; T3: 13.2+)

[d] Use of aspirin (including both low-dose and regular aspirin) defined by use over 10 years prior to baseline

[e] Use of non-aspirin NSAID (including ibuprofen, naproxen, and celecoxib/rofecoxib) defined by use over 10 years prior to baseline

[f] 1 oz=28.35 g

Table 2

Hazard Ratios (HR) of Colorectal Cancer Associated with Use of Glucosamine, Glucosamine Plus Chondroitin, and Methylsulfonylmethane (MSM) Supplements over the 10 Years Prior to Baseline

Supplement Use	Cohort	Cases	Age and Sex Adjusted		Multivariate Adjusted[a]	
	N (%)	N (%)	HR	95% CI	HR	95% CI
Glucosamine[b]						
No Use of Glucosamine, Chondroitin, MSM	59,024 (79.6)	461 (83.2)	1.00	Ref	1.00	Ref
Low Use (<4 days/week or <3 yrs)	9,724 (13.1)	63 (11.4)	0.79	0.61, 1.03	0.98	0.72, 1.32
High Use (≥4 days/week and ≥3 years)	5,395 (7.28)	30 (5.42)	0.62	0.43, 0.89	0.71	0.46, 1.11
			P-trend: 0.003		*P-trend: 0.19*	
Glucosamine Alone[c]						
No Use of Glucosamine, Chondroitin, MSM	59,024 (93.3)	461 (94.5)	1.00	Ref	1.00	Ref
Low Use (<4 days/week or <3 years)	3,022 (4.78)	21 (4.30)	0.88	0.57, 1.37	1.04	0.63, 1.73
High Use (≥4 days/week and ≥3 years)	1,229 (1.94)	6 (1.23)	0.56	0.25, 1.26	0.86	0.38, 1.94
			P-trend: 0.15		*P-trend: 0.84*	
Glucosamine Plus Chondroitin[d]						
No Use of Glucosamine, Chondroitin, MSM	59,024 (85.5)	461 (88.0)	1.00	Ref	1.00	Ref
Low Use (<4 days/week or <3 years)	6,509 (9.43)	44 (8.40)	0.81	0.59, 1.11	1.07	0.75, 1.51
High Use (≥4 days/week and ≥3 years)	3,481 (5.04)	19 (3.63)	0.60	0.38.0.95	0.55	0.30, 1.01
			P-trend: 0.01		*P-trend: 0.16*	
Methylsulfonylmethane (MSM)[e]						
No Use of Glucosamine, Chondroitin, MSM	59,024 (94.2)	461 (96.4)	1.00	Ref	1.00	Ref
Low Use (<4 days/week or <3 years)	2,852 (4.55)	12 (2.51)	0.51	0.29, 0.91	0.72	0.39, 1.32
High Use (≥4 days/week and ≥3 years)	753 (1.20)	5 (1.05)	0.79	0.33, 1.90	0.48	0.12, 1.94
			P-trend: 0.05		*P-trend: 0.14*	

Abbreviations: HR (hazard ratio); MSM (methylsulfonylmethane); 95% CI (95% confidence interval)

[a]Multivariate model adjusted for age, sex, race/ethnicity, education, BMI, energy intake, MET-hours per week of moderate/vigorous activity, alcohol intake, smoking history, multivitamin use, calcium intake (diet+supplement), dietary fiber intake, fruit and vegetable intake (excluding potatoes), red/processed meat intake, aspirin use, non-aspirin NSAID use, family history of colorectal cancer, history of sigmoidoscopy/colonoscopy, history of polyp excision, hormone replacement therapy, and history of arthritis or joint pain

[b]High/low use of glucosamine defined by use of glucosamine, regardless of whether participant also used chondroitin and/or MSM

[c] High/low use of glucosamine alone defined by use of glucosamine only; participants using glucosamine in addition to chondroitin and/or MSM are excluded from analyses

[d] Users of glucosamine alone or chondroitin alone excluded from these analyses

[e] 83% of users of MSM are also users of glucosamine or chondroitin.

Table 3

Hazard Ratios (HR) of Colorectal Cancer Associated with Use of Glucosamine Plus Chondroitin, by Sex, Aspirin Use, Body Mass Index, Cancer Subsite, and Stage

	10-yr Use of Glucosamine Plus Chondroitin Supplements										
	No Use			Low Use (<4 days/week or <3 yrs)			High Use (≥4 days/week and ≥3 yrs)				
	Case/Cohort	HR[b]	95% CI	Case/Cohort	HR[b]	95% CI	Case/Cohort	HR[b]	95% CI	P-trend	P-interaction[c]/P-difference[d]
Sex											
Male	209/25,114	1.00	Ref	11/2,075	0.71	0.38, 1.32	5/1,234	0.51	0.21, 1.26	0.08	0.19
Female	136/21,618	1.00	Ref	27/3,306	1.41	0.91, 2.17	6/1,606	0.63	0.27, 1.46	0.94	
Aspirin Use[e]											
Not regular	208/26,194	1.00	Ref	26/2,631	1.44	0.94, 2.22	6/1,288	0.57	0.25, 1.30	0.78	0.19
Regular	137/20,538	1.00	Ref	12/2,750	0.68	0.37, 1.25	5/1,552	0.50	0.20, 1.24	0.07	
Body Mass Index											
<25 kg/m^2	96/15,831	1.00	Ref	14/1,840	1.49	0.83, 2.68	7/948	1.14	0.51, 2.52	0.40	0.006
≥25 kg/m^2	249/30,901	1.00	Ref	24/3,541	0.92	0.60, 1.43	4/1,892	0.28	0.10, 0.76	0.02	
Subsite[f]											
Colon	256/46,732	1.00	Ref	28/5,381	1.02	0.68, 1.53	9/2,840	0.57	0.29, 1.13	0.20	0.56
Rectum	89/46,732	1.00	Ref	10/5,381	1.24	0.63, 2.45	2/2,840	0.45	0.11, 1.85	0.54	
Stage[g]											
Local	160/46,547	1.00	Ref	14/5,357	0.84	0.48, 1.48	4/2,833	0.42	0.15, 1.16	0.09	0.19
Regional/Distant	181/46,568	1.00	Ref	23/5,366	1.23	0.78, 1.93	7/2,836	0.66	0.31, 1.44	0.68	

Abbreviations: HR (hazard ratio); 95% CI (95% confidence interval)

[a] Users of glucosamine alone or chondroitin alone excluded from these analyses

[b] Multivariate model adjusted for age, sex, race/ethnicity, education, BMI, energy intake, MET-hours per week of moderate/vigorous activity, alcohol intake, smoking history, multivitamin use, calcium intake (diet+supplement), dietary fiber intake, fruit and vegetable intake (excluding potatoes), red/processed meat intake, aspirin use, non-aspirin NSAID use, family history of colorectal cancer, history of sigmoidoscopy/colonoscopy, history of polyps, hormone replacement therapy, and history of arthritis or joint pain

[c] P-interaction used to test for effect modification by sex, aspirin use, and body mass index

[d] P-difference used to test for differences across cancer subsite and stage

[e] Regular use of aspirin (including both low-dose and regular aspirin) defined as use at least once a week for a year over the 10 year period prior to baseline

[f] Cancers of the subsite not under study included in subsite-stratified analyses and censored at date of diagnosis

[g] Cancers of stages not under study excluded from stage-stratified analyses

Table 4

Sensitivity Analysis: Association between Glucosamine+Chondroitin Use and CRC, Within the First and Second

	First Half of Follow-up[a]				Second Half of Follow-up[b]			
	Cohort	Cases	Multivariate Adjusted[c]		Cohort	Cases	Multivariate Adjusted[c]	
Supplement Use	**N (%)**	**N (%)**	**HR**	**95% CI**	**N (%)**	**N (%)**	**HR**	**95% CI**
Glucosamine Plus Chondroitin[d]								
No Use of Glucosamine, Chondroitin, MSM	59,024 (85.5)	236 (91.1)	1.00	Ref	54,999 (85.4)	225 (84.9)	1.00	Ref
Low Use (<4 days/week or <3 years)	6,509 (9.43)	18 (6.95)	0.82	0.48, 1.41	6,134 (9.52)	26 (9.81)	1.33	0.85, 2.10
High Use (≥4 days/week and ≥3 years)	3,481 (5.04)	5 (1.93)	0.28	0.09, 0.89	3,279 (5.09)	14 (5.28)	0.85	0.41, 1.76
			P-trend: 0.03				*P-trend: 0.80*	

Half of Follow-up

Abbreviations: HR (hazard ratio); 95% CI (95% confidence interval)

[a] First half of follow-up defined by the first 3.5 years of each participant's follow-up

[b] Second half of follow-up includes follow-up beyond the first 3.5 years of each participant's follow-up

[c] Multivariate model adjusted for age, sex, race/ethnicity, education, BMI, energy intake, MET-hours per week of moderate/vigorous activity, alcohol intake, smoking history, multivitamin use, calcium intake (diet+supplement), dietary fiber intake, fruit and vegetable intake (excluding potatoes), red/processed meat intake, aspirin use, non-aspirin NSAID use, family history of colorectal cancer, history of sigmoidoscopy/colonoscopy, history of polyp excision, hormone replacement therapy, and history of arthritis or joint pain

[d] Users of glucosamine alone or chondroitin alone excluded from these analyses