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## Glucosamine Use and Risk of Colorectal Cancer: Results from the Cancer Prevention Study II Nutrition Cohort

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### Abstract

**Purpose**—Use of glucosamine supplements has been associated with reduced risk of colorectal cancer (CRC) in previous studies; however, information on this association remains limited.

**Methods**—We examined the association between glucosamine use and colorectal cancer risk among 113,067 men and women in the Cancer Prevention Study II Nutrition Cohort. Glucosamine use was first reported in 2001 and updated every two years thereafter. Participants were followed from 2001 through June of 2011, during which time 1440 cases of CRC occurred.

**Results**—As has been observed in prior studies, current use of glucosamine, modeled using a time-varying exposure, was associated with lower risk of colorectal cancer (HR: 0.83; 95% CI: 0.71, 0.97) compared to never use. However, for reasons that are unclear, this reduction in risk was observed for shorter-duration use (HR: 0.68, 95% CI: 0.52–0.87 for current users with  $\geq 2$  years use) rather than longer-duration use (HR: 0.90, 95% CI: 0.72–1.13 for current users with 3–<6 years of use; HR: 0.99, 95% CI: 0.76–1.29 for current users with  $\geq 6$  years of use).

**Conclusions**—Further research is needed to better understand the association between glucosamine use and risk of colorectal cancer, and how this association may vary by duration of use.

### Keywords

chemoprevention; colorectal cancer; dietary supplements; epidemiology; glucosamine

### INTRODUCTION

Glucosamine is a non-vitamin, non-mineral specialty supplement commonly taken for osteoarthritis. It is one of the most commonly used specialty supplements among US adults,

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with recent work indicating that 3.4% of US adults ages 40–64y reported use of this supplement in the prior 30 days in 2011–2012, as compared to 8.5% of adults ages 65+ [1]. Although the effectiveness of glucosamine for osteoarthritis remains controversial [2, 3], epidemiologic evidence suggests that use is associated with reduced risk of colorectal cancer [4–6]. In an exploratory analysis conducted within the VITamins And Lifestyle (VITAL) study, glucosamine use was associated with a 27% reduced risk of colorectal cancer (CRC) (HR: 0.73; 95% CI: 0.54, 0.98) [4]. We recently replicated this finding in the Nurses' Health Study and Health Professionals Follow-up Study wherein use of glucosamine was associated with a 21% reduced risk of CRC (HR: 0.79; 95% CI: 0.63, 1.00) [6]. Although the mechanism underlying this inverse association is unclear, there is a growing body of *in vitro*, animal, and human evidence suggesting that glucosamine may have anti-inflammatory properties [7–27]. Given that inflammation is implicated in the etiology of CRC [28–32], this may represent a plausible biologic mechanism by which glucosamine use could reduce risk of CRC.

Given the accumulating, albeit limited, body of evidence to support a potential chemopreventive effect, we sought to examine the association between use of glucosamine and CRC risk in the Cancer Prevention Study-II (CPS-II) Nutrition Cohort. Since this large cohort assessed glucosamine use at multiple time points, it offered the opportunity to account for changing patterns of glucosamine use over time using a time-varying exposure, and allowed us to assess associations by duration of use.

## MATERIALS AND METHODS

### Study population

This study was conducted using data from the Cancer Prevention Study (CPS)-II Nutrition Cohort. Men and women in the CPS-II Nutrition Cohort (n=184,185) were recruited from the 1.2 million US adults enrolled in the CPS-II Baseline Cohort, a study of cancer mortality [33]. During 1992 and 1993, a detailed questionnaire was mailed to a subgroup of CPS-II Baseline Cohort participants; those who returned the questionnaire were enrolled in the Nutrition Cohort, as described previously [33]. Participants in the Nutrition Cohort are followed for cancer incidence and mortality and have received additional mailed questionnaires in 1997 and every 2 years thereafter. In these subsequent questionnaires, participants provided updated information on both exposures and outcomes of interest.

A total of 128,851 CPS-II Nutrition Cohort participants returned the long-form of the 2001 questionnaire, the first questionnaire that included glucosamine. We excluded those with a history of CRC prior to 2001 (n=3,245), those who were lost to follow-up (n=3,162), those whose self-reported CRC on the first follow-up survey could not be verified through medical records or registry linkage (n=84), those with inflammatory conditions (rheumatoid arthritis, ulcerative colitis, and Crohn's disease; n=8,205), as well as those without sufficient information to determine exposure category for the glucosamine variable (n=1,088). After making these exclusions, 113,067 persons remained in the analyses.

## Exposure assessment

Participants were first asked about use of glucosamine in 2001, considered ‘baseline’ for this analysis. At this time, participants were asked to report whether or not they currently used glucosamine supplements or had/had not used glucosamine supplements only in the past. Those who reported current use were then asked to report the frequency (1–3 days/week, 4–6 days/week, or 7 days/week) and duration of use (0–2 years, 3–5 years, or ≥6 years). This information was used to create the variable: never use; former use/occasional use (with occasional use defined as use <4 days/week); and current regular use (defined as use on ≥4 days/week). This threshold was selected to capture a frequency of use that may plausibly act to biologically affect cancer risk, based on studies of other anti-inflammatory agents (e.g. aspirin) in relation to cancer risk. This cutpoint was also applied in prior studies of glucosamine and cancer risk, including studies of colorectal cancer [5, 34–36]. We also created a variable to capture duration of use, categorized as: never use; former/occasional use, with <2 years of use; and current regular use, with ≥3 years of use. Chondroitin, a supplement commonly included with glucosamine in joint health supplement formulations, was not included on the questionnaire.

The 2003, 2005, 2007, and 2009 questionnaires included information on supplement use. From this information, we created updated (i.e. time-varying) exposure variables that accounted for changes in use after baseline. For example, for the current/former/never variable, a participant who reported use in 2001, but no use in 2003, would be reclassified as a former user in 2003. In the updated duration analyses (also modeled using a time-varying exposure), participants continued to accrue exposure time if they continued to report usage. If they discontinued use, they would become a former user at that time. In the updated duration analyses, the number of persons reporting several years of use was sufficient to examine higher categories of duration than was possible in analyses of baseline exposure. Specifically, in analyses of updated exposure, we were able to separately examine associations for current regular users reporting 3–<5 years of use and current regular users reporting ≥6 years of use. In all updated analyses, if information on use was missing, it was assumed that exposure was the same as in the prior questionnaire. However, if information on exposure was missing on two questionnaires in a row, the participant was censored at the time of the second questionnaire.

## Outcome ascertainment

This analysis included 1,440 incident colorectal cancers diagnosed between the return of the 2001 questionnaire and June 30, 2011. Of these, 1,155 were initially identified by self-report on follow-up questionnaires and were subsequently verified by obtaining medical records (N=888) or through linkage with cancer registries when medical records could not be obtained (N=267). An additional 285 cases were initially identified through linkage to the National Death Index (NDI) [37], of which 152 were subsequently verified through linkage with cancer registries.

## Statistical analysis

Cox proportional hazards regression estimated hazard ratios (HR) and corresponding 95% confidence intervals (95% CI), with study time as the time axis. Follow-up for the Cox

models began on the date of completion of the 2001 questionnaire. In all Cox models, the stratified Cox procedure was used to adjust for age within 1-year strata [38]. Covariates were selected *a priori*, and include those variables hypothesized to be associated with both the exposure (glucosamine use) and outcome (risk of CRC). Age- and sex-adjusted analyses are presented, as are multivariable-adjusted models, which further include the following: race (white, black, other), education (<high school, high school graduate, some college, college graduate), BMI (kg/m<sup>2</sup>: <22.5, 22.5-<25, 25-<27.5, 27.5-<30, 30), physical activity (metabolic equivalent of task [MET]-hrs/week: <3.5, 3.5-<4.5, 4.5-<14, 14-<21.5, 21.5), smoking (never, current, former and quit <10 years ago, former and quit 10 years ago, former and quit unknown years ago), alcohol (drinks/day: no use, <1, 1), red/processed meat (g/day: quartiles), total calcium (mg/day: quartiles), total fiber (g/day: quartiles), total folate (mcg/day: quartiles), vitamin D (IU/day: quartiles), energy intake (kcal/day: quartiles), multivitamin use (no use, current use with use <6 pills/week, current use with use of 6 pills/week, current use with unknown pills/week), hormone replacement therapy (HRT) use (never, current, former), use of regular aspirin (no use, use of <20 pills/month, use of 20 pills/month), use of baby aspirin (no use, use of <20 pills/month, use of 20 pills/month), use of non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) (no use, 1-<15 pills/month, 15-<30 pills/month, 30-<60 pills/month, 60 pills/month), receipt of sigmoidoscopy/colonoscopy (never, ever), history of polyps (no yes), family history of CRC (no, yes), diabetes (no, yes), self-reported health status (excellent/very good, good, fair/poor), and osteoarthritis (no, yes). Covariates were assessed at baseline, with the exception of diet; dietary variables were not assessed in the 2001 questionnaire (baseline for this study), and therefore the following dietary covariates were ascertained using data from the 1999 questionnaire: alcohol, red/processed meat, calcium, fiber, folate, vitamin D, and energy intake. The calcium, folate, and vitamin D variables all include both dietary intake and supplemental intake. When status for a given covariate was unknown, a missing indicator was included.

Analyses were conducted to evaluate whether the association varied by baseline age (<70 years vs 70 years, to evaluate if the association varies for middle-aged adults as compared to older adults), sex, BMI (<25 kg/m<sup>2</sup> vs 25 kg/m<sup>2</sup>, to evaluate if the association varies for underweight/normal weight individuals, as compared to overweight and obese individuals), and baseline non-aspirin NSAID use (no vs yes, to evaluate if the association varies by use of these anti-inflammatories). Interaction was evaluated using a likelihood ratio test. We further examined associations by subsite (colon vs rectal) and stage at diagnosis (local, regional distant, unknown). Sensitivity analyses were conducted to better understand observed associations. Each sensitivity analysis is detailed in the Results Section of the text.

All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Carey, NC). The CPS-II Nutrition Cohort has been approved by the Emory University Institutional Review Board.

## RESULTS

In this study of 113,067 study participants, 1440 incident CRC cases were identified over an average of 8.3 years of follow-up. At baseline, 12,060 (10.7%) participants reported current

use of glucosamine on 4 days/week for 2 years and 6,279 (5.6%) reported current use on 4 days/week for 3 years.

Persons reporting current use of glucosamine for 3 years at baseline were more likely to be women than were never users (Table 1). Current long-term glucosamine users were also more likely than never users to be more educated and to have a history of colonoscopy/sigmoidoscopy. Current long-term glucosamine users were more likely to take multivitamins than never users, and also had a higher intake of calcium, fiber, folate, and vitamin D per calorie consumed (eTable 1). Compared to never users, long-term current glucosamine users were also more likely to report HRT use, non-aspirin NSAID use, and a history of osteoarthritis.

In age- and sex-adjusted analyses, current glucosamine use at baseline was associated with reduced risk of CRC (HR: 0.80; 95% CI: 0.68, 0.93) (Table 2); this association was attenuated with multivariable adjustment (HR: 0.88; 95% CI: 0.75, 1.03). When updating glucosamine use to account for changes in use after baseline using a time-varying exposure, the multivariable-adjusted association strengthened and became statistically significant (HR: 0.83; 95% CI: 0.71, 0.97). This association varied over time (p-interaction:0.006), with the association between updated glucosamine use and risk of colorectal cancer stronger in the first five years of follow-up (HR: 0.77; 95% CI: 0.62–0.95) than in later years (HR: 0.91; 95% CI: 0.73, 1.14) (data shown in text only). To better understand the change in association over the study and the potential interplay between study time and duration of use, a sensitivity analysis was conducted including both duration of use and a time interaction in the same model. In this model, the interaction weakened, but persisted (p-interaction: 0.03).

In analyses of duration (as reported at baseline), the multivariable-adjusted HR was lowest for persons reporting 2 years of use (HR: 0.82; 95% CI: 0.68, 1.00), whereas a null association was observed for persons reporting 3 years of use (HR: 0.99; 95% CI: 0.78, 1.26) (Table 2). When updating glucosamine use to account for changes in use after baseline using a time-varying exposure, the association was again strongest for those with 2 years of use (HR: 0.68; 95% CI: 0.52, 0.87), and weaker with increasing duration of use (HR<sub>3–5 years of use</sub>: 0.90; 95% CI: 0.72, 1.13; HR<sub>6 years of use</sub>: 0.99; 95% CI: 0.76, 1.29). To better understand the interplay of current glucosamine use and duration of use, we conducted a sensitivity analysis including both current use and a continuous variable for duration of use among current users in the same model; in this analysis, the p-value for duration of use was 0.02, supporting a difference in association by duration of use among current users (data shown in text only).

To further explore the association by duration and to better understand the timing of exposure, we conducted a sensitivity analysis lagging the time-varying exposure by 2 years. In this sensitivity analysis, the association with glucosamine use disappeared, both in models of current use (HR<sub>current</sub>: 0.99; 95% CI: 0.83, 1.17) and in models presented in terms of duration of use (HR<sub>2 years of use</sub>: 0.93; 95% CI: 0.72, 1.19; HR<sub>3–5 years of use</sub>: 1.02; 95% CI: 0.80, 1.30); (HR<sub>6 years of use</sub>: 1.05; 95% CI: 0.75, 1.45) (data shown in text only).

For cases identified only by the NDI only, it is possible that exposures were evaluated after the onset of disease (when behaviors and glucosamine use might have changed as a result of disease). To address concern about reverse causality among these NDI-identified cases, we conducted a sensitivity analysis excluding these cases. This sensitivity analysis revealed the same pattern of association that was observed in our current use analyses, as well as our duration of use analyses.

No significant interactions were observed between duration of glucosamine use and stratification variables (age, sex, BMI, and non-aspirin NSAID use) (eTable 2). There were no marked differences in association by subsite and stage, although power was very limited in subgroup analyses (eTable 3).

Lastly, given concern that screening may blunt the natural history of disease, we conducted sensitivity analyses restricted to never-screened individuals (includes 21,373 never screened as of baseline, further censoring participants at the date of first screen). In these sensitivity analyses, a non-significant inverse association was observed in analyses of current use as reported at baseline (HR<sub>current</sub>: 0.80; 95% CI: 0.54, 1.17). In contrast to the main analysis, the inverse association between baseline glucosamine use and risk of CRC did not show evidence of attenuating with increasing duration of use: a non-significant inverse association was observed in both short-term and long-term users. Among those reporting 2 years of use, an HR of 0.79 (95% CI: 0.51, 1.24) was observed, and among those reporting 3 years of use, an HR of 0.80 (95% CI: 0.42, 1.53) was observed (data shown in text only).

## DISCUSSION

In the CPS-II Nutrition Cohort, current use of glucosamine supplements, updated to account for changes in use after the baseline assessment, was associated with an estimated 17% lower risk of CRC. However, this association was driven by shorter duration use, whereas there was no association with longer duration use.

The overall inverse association between glucosamine use and risk of CRC observed in this analysis of the CPS-II Nutrition Cohort is generally consistent with those observed in the VITAL study [4] and the NHS/HPFS [6]. Specifically, in the VITAL study, any use of glucosamine at baseline was associated with a 27% reduced risk of CRC [4]. In the NHS/HPFS, current regular use of glucosamine at baseline was associated with a 21% reduced risk of CRC [6].

In this study, we observed an inverse association only with short, and not long, duration use. This was true for models of both baseline and updated exposures. These results suggest that the inverse association with CRC may be limited to the first few years after glucosamine use is initiated. Neither of the two previous cohort studies specifically examined duration of glucosamine use among regular users. However, in the VITAL cohort, high frequency and high duration of use (4 days/week for 3 years over the ten years prior to baseline) was associated with a non-significant lower risk of CRC (HR 0.71, 95% CI 0.46, 1.11) whereas infrequent and/or short-term use (<4 days/week or <3 years of the ten years prior to baseline) was not associated with risk (HR: 0.98; 95% CI 0.72, 1.32) [5].

It is unclear why short, but not long, duration of glucosamine use was associated with lower risk of CRC in the CPS-II Nutrition Cohort. Chance cannot be entirely ruled out. However, the p-value for a difference in the HR by duration of use among current users was relatively low ( $p = 0.02$ ). Confounding also cannot be ruled out. However, for confounding to explain the observed associations, compared to shorter duration users, long duration glucosamine users would have to have higher prevalence of unmeasured or imperfectly measured colorectal cancer risk factors. Our data indicate that this is unlikely to be the case: in general, longer duration users were *less* likely than shorter duration users to have colorectal risk factors such as lower levels of physical activity or screening. Longer duration users were slightly more likely than shorter duration users to report osteoarthritis, but reported osteoarthritis was not significantly associated with colorectal cancer risk in this cohort. Longer duration users were also more likely than shorter duration users to be obese. Even so, the difference in the prevalence of obesity was relatively small, making meaningful residual confounding by obesity unlikely. Furthermore, it is unlikely that there are unmeasured confounders strong enough to explain the observed results, given that the CPS-II Nutrition Cohort collects data on known CRC risk factors, which we have included in our models. It is also possible that glucosamine might only temporarily delay late stages of colorectal cancer progression, resulting in a transient reduction in risk following initiation of glucosamine use. However, we are not aware of a specific biological mechanism that supports a transient effect of glucosamine on any particular stage of colorectal carcinogenesis. Lastly, most participants in this study reported a prior history of sigmoidoscopy/ colonoscopy. It is possible that screening may obfuscate the time relation by removing adenomas and biasing the cancers diagnosed largely to those that escape screening or are fast growing. In sensitivity analyses restricted to the never screened population (censoring at first screen), we found that the pattern did not indicate that the association was stronger for short duration of use than longer duration of use, as was observed in the main analyses. However, these sensitivity analyses were very limited in power given the small number of never-screened individuals, limiting the interpretation of these findings. Further research is needed to determine if the association of glucosamine with CRC varies by duration, and if so, what might explain this pattern of results.

Sensitivity analyses revealed that the association between updated glucosamine use and CRC risk varied over follow-up, with the association stronger in the first half of follow-up than the second half of follow-up. Further sensitivity analyses revealed that the interaction between current glucosamine use and study time was not entirely explained by the shift towards longer duration use in later follow-up, as inclusion of both a duration variable and a time interaction in the same model did not completely eliminate the interaction. This pattern of association, indicating that the association between glucosamine use and risk of CRC weakens over time, is consistent with a follow-up analysis of the VITAL findings [5]. In the VITAL follow-up study, it was proposed that the association became weaker with time due to the use of a single baseline exposure measure, rather than repeated measures (given hypothesized increased measurement error over time due to temporal changes in use in the population and aging of the cohort). However, this pattern of association was observed in the current study even when using a time-varying, updated 'current use' exposure variable. It therefore seems unlikely that this pattern of association is due to participants initiating or

discontinuing use over the course of the study, although it is possible that temporal changes in the dose or formulation may cause the association to weaken over time. However, the explanation underlying this pattern of results remains unclear and merits further follow-up.

It is hypothesized that glucosamine might reduce risk through an anti-inflammatory mechanism. Specifically, *in vitro* studies suggest that glucosamine reduces inflammation through the inhibition of nuclear factor kappa B (NFkB), a transcription factor central to the inflammatory cascade. NFkB lies upstream of several inflammatory factors, including several cytokines that affect cell growth, proliferation, and survival [39]. In animal studies, glucosamine administration has been found to reduce markers of inflammation downstream of NFkB [16–22, 26], while also reducing NFkB expression in the colonic mucosa [22], providing evidence to support a biologic effect in the colon. Four human studies, including two small trials, suggest that this anti-inflammatory effect may extend to humans [23–25, 27].

A notable strength of this study is the large sample size, which enabled us to conduct a well-powered study. Importantly, we also had updated information on glucosamine use during follow-up, allowing us to account for changes in use over the study period (modeling use as a time-varying exposure). This is especially important for study of glucosamine, given the changing popularity of this supplement over time [40]. Further, we were able to conduct analyses examining results by duration of use, a question that could not be addressed as thoroughly elsewhere.

Some limitations of this analysis should also be noted. Despite the large sample size, we were still limited with duration-specific and stratified analyses. Importantly, no information was available on whether glucosamine supplements also included chondroitin, which is often coupled with glucosamine in joint health supplements. It is possible that the observed association between glucosamine and CRC may be driven by chondroitin or by the combination of glucosamine and chondroitin supplements, as has been suggested by some of our prior work [5, 6, 23, 41]. Furthermore, it should be noted that in duration-specific analyses, even the long-duration group is not that long (especially in analyses of baseline glucosamine use). This is relevant, given that use of the anti-inflammatory, aspirin, takes several years to reduce risk of CRC [32]. Furthermore, the assessment of glucosamine changed slightly over the years, which may have induced some measurement error in the updated analyses. However, this is a minimal concern, given that the pattern of results were comparable in analyses of both baseline and updated glucosamine use. Lastly, this study was conducted in a population in which most individuals have received a prior endoscopy. A larger never-screened population would be needed to understand the association of glucosamine with colorectal cancer risk in the absence of endoscopic screening.

In summary, while results of this study suggest a potential inverse association between glucosamine use and risk of CRC, it is critically important that we better understand the association by duration and timing of use. Such information will help us better understand if this association is likely to be causal, and if so, when glucosamine may act in the process of colorectal carcinogenesis. There is great need to identify safe, effective, and easily



implemented strategies to prevent colorectal cancer, and further research is needed to inform our understanding of the chemopreventive potential of glucosamine supplements.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**

Selected Age-and Sex-Adjusted Characteristics, by Duration of Glucosamine Use, as Reported at Baseline

Population Characteristics <sup>a</sup>	Baseline Glucosamine Use			
	Never	Former/Occasional <sup>b</sup>	Current, <sup>c</sup> 2 yrs	Current, <sup>c</sup> 3 yrs
	N=86,777 %	N=7,951 %	N=12,060 %	N=6,279 %
<b>Sociodemographic</b>				
Age (yrs)				
<65	13.9	15.0	14.9	13.4
65–<70	25.5	26.0	28.0	27.7
70–<75	29.0	29.4	29.8	31.3
75–<80	21.8	21.1	19.9	20.5
80	9.7	8.5	7.3	7.0
Sex				
Female	53.8	68.3	62.3	60.5
Male	46.2	31.7	37.7	39.5
Race				
White	97.7	97.7	98.1	98.5
Black	1.2	1.0	0.6	0.4
Other/Unknown	1.2	1.3	1.3	1.1
Education				
<High School	5.2	4.2	3.3	2.7
High School Graduate	25.9	20.2	21.1	18.9
Some College	28.1	29.6	28.5	29.0
College Graduate	40.1	45.6	46.4	49.0
Unknown	0.6	0.5	0.7	0.4
<b>Lifestyle Factors</b>				
BMI (kg/m <sup>2</sup> )				
<22.5	19.8	15.8	17.1	17.3
22.5–<25	23.0	22.3	22.7	22.8
25–<27.5	23.5	23.9	24.2	24.1
27.5–<30	13.6	14.7	14.4	14.4
30	15.1	19.0	17.0	17.7
Unknown	5.1	4.4	4.5	3.8
Physical Activity (METs/wk)				
<3.5	14.6	14.2	11.6	10.8
3.5–<4.5	11.0	10.6	9.4	8.0
4.5–<14	24.8	25.4	24.5	24.0
14–<21.5	20.2	19.5	21.0	21.2
21.5	27.0	28.5	31.6	34.2

Population Characteristics <sup>a</sup>	Baseline Glucosamine Use			
	Never	Former/Occasional <sup>b</sup>	Current, <sup>c</sup> 2 yrs	Current, <sup>c</sup> 3 yrs
	N=86,777 %	N=7,951 %	N=12,060 %	N=6,279 %
Unknown	2.5	1.8	2.0	1.7
Smoking Status				
Never	44.9	43.5	45.4	45.0
Current	4.4	2.8	2.2	1.9
Former, Quit <10 yrs ago	5.3	4.7	3.7	4.0
Former, Quit 10 yrs ago	41.8	45.6	45.3	46.1
Former, Quit, unknown yrs	0.3	0.3	0.2	0.2
Unknown	3.4	3.1	3.1	2.8
<b>Medication Use</b>				
Current Use of Regular Aspirin				
No Use	67.4	70.3	69.6	70.4
<20 pills/month	10.5	11.2	10.6	10.4
20 pills/month	17.0	15.4	16.5	16.8
Unknown	5.2	3.1	3.3	2.4
Current Use of Baby Aspirin				
No use	68.1	69.2	67.8	66.0
<20 pills/month	3.7	4.2	3.7	4.2
20 pills/month	21.6	22.0	24.3	26.7
Unknown	6.5	4.5	4.2	3.1
Current Use of Non-aspirin NSAIDs				
No use	69.3	50.4	52.6	49.2
1–<15 pills/month	12.3	15.4	14.8	15.0
15–<30 pills/month	3.5	5.9	5.8	6.1
30–<60 pills/month	6.7	14.7	13.3	15.4
60 pills/month	4.4	10.4	10.3	11.7
Unknown	3.9	3.1	3.2	2.5
<b>Screening, Health History, and Other Risk Factors</b>				
Endoscopy/Sigmoidoscopy				
Never	19.7	16.8	16.8	15.2
Ever	68.4	74.3	73.7	76.2
Unknown	11.9	8.9	9.6	8.6
Self-Reported Health Status				
Excellent/very good	49.2	46.2	51.0	53.7
Good	34.4	36.3	35.7	33.7
Fair/poor	10.5	11.7	7.7	7.5
Unknown	6.0	5.8	5.6	5.1
History of Osteoarthritis				

Population Characteristics <sup>a</sup>	Baseline Glucosamine Use			
	Never	Former/Occasional <sup>b</sup>	Current, <sup>c</sup> 2 yrs	Current, <sup>c</sup> 3 yrs
	N=86,777 %	N=7,951 %	N=12,060 %	N=6,279 %
No	86.9	63.5	67.1	59.1
Yes	13.1	36.5	32.9	40.9

BMI (body mass index); HRT (hormone replacement therapy); NSAIDs (non-steroidal anti-inflammatory drugs); MET (metabolic equivalent of task)

<sup>a</sup>All population characteristics are age and sex-adjusted, with the exception of age (only sex-adjusted) and sex (only age-adjusted)

<sup>b</sup>Occasional use defined as use <4 days/week

<sup>c</sup>Current use defined by current use on 4 days/week

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Association between glucosamine use and risk of colorectal cancer in the Cancer Prevention Study (CPS)-II Nutrition Cohort

Table 2

Exposure	Cases		Person-years		Age- and Sex-Adjusted		Multivariable-Adjusted <sup>a</sup>	
	N		HR	95% CI	HR	95% CI	HR	95% CI
<b>Baseline Variables<sup>b,c</sup></b>								
Current glucosamine								
Never Use	1,148	708,990	1.00	Ref	1.00	Ref	1.00	Ref
Former/Occasional	97	66,939	0.96	0.78, 1.18	1.02	0.82, 1.26	1.02	0.82, 1.26
Current	195	158,267	0.80	0.68, 0.93	0.88	0.75, 1.03	0.88	0.75, 1.03
Duration of glucosamine use								
Never Use	1,148	708,990	1.00	Ref	1.00	Ref	1.00	Ref
Former/Occasional	97	66,939	0.96	0.78, 1.18	1.02	0.82, 1.26	1.02	0.82, 1.26
Current: 2 years	121	104,079	0.76	0.63, 0.91	0.82	0.68, 1.00	0.82	0.68, 1.00
Current: 3 years	74	54,188	0.88	0.69, 1.11	0.99	0.78, 1.26	0.99	0.78, 1.26
<b>Updated Time-varying Variables<sup>c,d</sup></b>								
Current glucosamine								
Never Use	1,034	617,130	1.00	Ref	1.00	Ref	1.00	Ref
Former/Occasional	164	119,846	0.90	0.76–1.06	0.95	0.80, 1.13	0.95	0.80, 1.13
Current	210	178,254	0.75	0.65–0.88	0.83	0.71, 0.97	0.83	0.71, 0.97
Duration of glucosamine use								
Never Use	1,034	617,130	1.00	Ref	1.00	Ref	1.00	Ref
Former/Occasional	164	119,846	0.90	0.76, 1.06	0.96	0.81, 1.14	0.96	0.81, 1.14
Current: 2 years	64	63,228	0.62	0.48, 0.80	0.68	0.52, 0.87	0.68	0.52, 0.87
Current: 3–5 years	83	65,743	0.81	0.64, 1.01	0.90	0.72, 1.13	0.90	0.72, 1.13
Current: 6 years	63	49,282	0.87	0.67, 1.12	0.99	0.76, 1.29	0.99	0.76, 1.29

<sup>a</sup>Multivariable-adjusted models adjusted for the following: age, sex, race, education, body mass index, physical activity, smoking, alcohol, red/processed meat, calcium, fiber, folate, vitamin D, energy intake, multivitamin use, HRT use, use of regular aspirin, use of baby aspirin, use of non-aspirin NSAIDs, family history of CRC, screening, history of polyps, diabetes, health status, and osteoarthritis.

<sup>b</sup>Baseline use is defined by use as reported in the 2001 questionnaire

<sup>c</sup>Current use defined by current use on 4 days/week

Updated variables incorporate information collected in follow-up questionnaires collected in 2003, 2005, 2007, and 2009.

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