Chondroitin Sulphate and Glucosamine Use Depend on Nonsteroidal Anti-inflammatory Drug Use to Modify the Risk for Colorectal Cancer

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ABSTRACT

Background: A safe and effective colorectal cancer chemoprevention agent remains to be discovered. There is little evidence regarding the protective effect of chondroitin sulphate and glucosamine on colorectal cancer. We aimed to assess the association between colorectal cancer risk and the use of chondroitin sulphate and glucosamine using a large cohort with dispensed data.

Methods: We performed a population-based case–control study in Catalonia using primary care reimbursed medication records (SIDIAP database). The study included 25,811 cases with an incident diagnosis of colorectal cancer and 129,117 matched controls between 2010 and 2015.

Results: The prevalence of ever use was 9.0% ($n = 13,878$) for chondroitin sulphate, 7.3% ($n = 11,374$) for glucosamine, and 35% for regular use of nonsteroidal anti-inflammatory drugs (NSAID; $n = 45,774$). A decreased risk of colorectal cancer was observed among chondroitin sulphate use [OR: 0.96; 95% confidence interval (CI), 0.91–1.01], glucosamine use (OR: 0.92; 95% CI, 0.87–0.97), and concurrent use of chondroitin sulphate and glucosamine (OR: 0.83; 95% CI, 0.70–0.98). Especially for glucosamine, there was a dose–response association regarding duration and cumulative dose. The analysis stratified by simultaneous use with other NSAIDs showed that these drugs used without other NSAIDs do not reduce risk (OR: 1.06; 95% CI, 0.74–1.51). However, they may have a synergistic protective effect when used with other NSAIDs (OR: 0.80; 95% CI, 0.72–0.88).

Conclusions: This study does not provide strong support for an independent protective association of chondroitin sulphate or glucosamine on colorectal cancer risk in our population. However, these drugs may have a synergistic beneficial effect among NSAID users.

Impact: Chondroitin sulphate or glucosamine may contribute to the protective effect of NSAID use in colorectal cancer.

Introduction

A large body of evidence has shown that nonsteroidal anti-inflammatory drugs (NSAID), particularly acetylsalicylic acid (ASA), reduce the risk of colorectal cancer and adenomas (1–4). Although the exact mechanism of action of NSAIDs in cancer prevention is unclear, the inhibition of production of prostaglandins by suppressing COX-2 might be, at least partly, responsible for their chemopreventive effects. This COX-2 inactivation, which is irreversible with ASA and reversible with NSAIDs, has been shown to decrease tumor growth and angiogenesis (5–8). However, NSAIDs are not generally recommended in the average-risk population to prevent colorectal cancer because COX-1 and -2 inhibitions increase the risk of gastrointestinal complications and cardiovascular disease (2, 9).

Glucosamine and chondroitin sulfate, sometimes consumed in combination, are commonly used in osteoarthritis to alleviate pain and inflammation (10). Recent evidence suggests that glucosamine and chondroitin sulfate supplements could reduce colorectal cancer risk (11–15). These drugs have been shown to reduce the NFκβ translocation, which has a clear role in the coordination of immune responses, cell-cycle regulation, and in tumorigenesis (16, 17). This mechanism may explain the possible chemopreventive effect, while the evidence also suggests that these drugs have a long-term safe profile with few side effects (18, 19).

There have been many randomized controlled trials assessing drugs and nutritional agents for the chemoprevention of colorectal cancer and adenomatous polyps. To this day, there is no solid evidence that other nutrients such as folic acid, calcium, vitamin D, and antioxidants are effective in the chemoprevention of colorectal neoplasia in the general population (20, 21).

The United States Preventive Services Task Force (USPSTF), after a careful review of ASA evidence for the prevention of colorectal cancer, recommends low-dose ASA use in a specific scenario where not only would it prevent the risk of colorectal cancer but also cardiovascular disease (1). The USPSTF's recommendation for ASA use is in adults from 50 to 69 years who have a life expectancy of at least 10 years, a 10% or greater 10-year cardiovascular risk, are not at increased risk for

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bleeding, and are willing to take low-dose aspirin daily for at least 10 years (22). In line with this recommendation, Seaton and colleagues (23) reported that the subgroup of women who would benefit the most from ASA's chemoprevention effect would be those with any cardiovascular disease risk, no family history of colorectal cancer, or a history of colonoscopy with polypectomy. Although ASA is the agent with more evidence, general use is not recommended because of its adverse events (21, 24). Safety is particularly important in chemoprevention, as the intake of the drug will be prolonged, thus increasing the possibility of side effects.

In this national register-based case–control study, we aimed to examine the association between colorectal cancer risk and chondroitin sulfate and glucosamine, since one of the main advantages of glucosamine and chondroitin sulfate is their safety profile.

Materials and Methods

Data source

The selection of the subjects was performed using the Information System for Development of Primary Care Research (SIDIAP) database (www.sidiap.org; ref. 25). Study design has already been published (26, 27). Briefly, SIDIAP database comprises clinical information routinely collected by primary care professionals, hospital admissions, and dispensed prescriptions since 2005. Exposure to medications is obtained from pharmacies' claims for reimbursement to the Catalan Institute of Health which is the public system in Catalonia. It provides health care to 74% of the population (5.8 million people). The data was obtained on the specific drug prescribed, date and units of the drug withdrawn. Previous studies have evaluated the quality of SIDIAP data to study the epidemiology of health outcomes (28).

Research was performed in accordance with the ethical standards of the institution, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Ethics Committee for Clinical Research of IDIAP Jordi Gol approved the study protocol. Written informed consent was not obtained from the participating individuals, as the study was based on anonymized data routinely collected and the Ethics Committee cleared that requirement. Personal identifiers were removed to ensure the confidentiality of the data, as required by the Spanish Law for Data Protection and Confidentiality (15/1999, 13 December, Protección de Datos de Carácter Personal).

Study design

A population-based case–control study nested within the cohort of subjects that requested health services to the public health system in Catalonia was conducted. The eligible subjects were those registered in SIDIAP with at least one health care interaction in last 3 years (n = 5,830,562). The study period was from January 1, 2010 to December 31, 2015. This study was restricted to the adult population, aged 18 to 90 years (n = 4,664,450), and included all cases identified with an incident diagnosis of colon or rectum [codes C18, C19, and C20 of the International Classification of Diseases 10th Revision (ICD-10)]. Diagnoses of appendix cancer (C18.1) were excluded. To identify the diagnosis of colorectal cancer, we used the information collected in the official regional hospital discharge administrative database (CMDB). This database contained information on diagnostic and procedure codes for all hospital admissions in public hospitals of Catalonia region (29). We have previously shown that the case ascertainment procedure provided the expected number of colorectal cancer cases (27).

We obtained a random stratified sample of controls extracted from the same SIDIAP database. For each case, we randomly selected five controls from the set of all subjects in the database alive without prior colorectal cancer at the time of diagnosis of the case. The control was selected with the same gender, age (± 5 years), and health care region.

The disease index date of cases was defined as the earliest colorectal cancer diagnosis date registered. And, for controls, the index date of their matched case was applied. Data on comorbidities and drug use were truncated to the information recorded prior to the index date for cases and controls. The policy of SIDIAP regarding anonymized data extraction did not allow keeping the individual matching once the index date was assigned, so the dataset obtained had a frequency matched design.

Exposure variables

Dispensed drug use was assessed as binary variable (ever/never exposed) and quantitatively, regarding the number of doses and duration of the exposure since 2005. Drug exposures were censored one year before the index date to avoid the presence of a protopathic bias caused by changes in drug use before the diagnosis of colorectal cancer (30). Individuals who had at least one dispensation recorded were considered exposed. Because of exposure censoring, subjects that only used the drugs within the last 12 months were considered nonexposed. Drugs were coded using the Anatomical Therapeutic Chemical (ATC) classification, which for chondroitin sulfate is M01AX25 and for glucosamine is M01AX05. Patients were classified as exposed to oral NSAIDs if they had one prescription recorded with ATC codes M01AB, M01AC, M01AE02, M01AE03, M01AE04, M01AE14, M01AE17, and M01AH. Moreover, ASA (codes: N02BA and B01AC06) was included in the NSAIDs definition. Daily defined doses (DDD) for each exposure were calculated as the product of the number of units dispensed times the dose (in mg) and divided by the standard DDD (in mg) for each drug defined by the World Health Organization (14).

Measuring drug exposure in DDD is a way to interpret cumulative dose in a time scale. One DDD is the recommended daily dose for the most frequent indication of the drug. For chondroitin sulfate, the DDD is 1,200 mg and for glucosamine is 1,500 mg. If one subject has consumed 90 DDDs, it can be interpreted as if the average exposure duration was 3 months (90 days), although the real duration could be shorter if the real daily dose was higher or longer if the dose was lower or the use irregular.

We noticed a very high exposure (63%) to ibuprofen (M01AE01) among controls and 64% among cases during the study period. This high prevalence was very often occasional use as analgesic, which may not be enough to inhibit inflammation. For this reason, in the definition of NSAIDs exposure, we requested a minimum exposure of 100 DDDs to be considered exposed. To avoid a differential analysis for other NSAIDs that might also be used occasionally, we used this criterion for all the individual drugs used for at least 5% of our population study. The following drugs were specifically studied: ASA (N02BA and B01AC06), indomethacin (M01AB01), diclofenac (M01AB05), aceclofenac (M01AB16), ibuprofen (M01AE01), naproxen (M01AE02), dexketoprofen (M01AE17), and celecoxib (M01AH01). Cumulative DDDs were estimated as the sum of dispensed DDD of the drugs analyzed from January 1, 2010 to the index date. Concomitant use was defined as a combination of different drugs in the same calendar year.

Confounders

We identified a list of potential confounders that required adjustment in the analysis: age, gender, year of index date, region, body mass index (BMI), tobacco, alcohol, comorbidity conditions, NSAID use,

and socioeconomic status. The MEDEA socioeconomic deprivation score (31), divided into quintiles, was used to adjust for socioeconomic status. Chronic comorbidity diseases were divided into two sets. One set was those associated with colorectal cancer, but *a priori* not considered indications for anti-inflammatory drug use: hypertension, hyperuricemia, diabetes, dyslipidemia, cardiovascular disease, chronic lower respiratory diseases, extrapyramidal and movement disorders, episodic and paroxysmal disorders, mental and behavioral disorders, chronic kidney disease, heart failure, cerebrovascular disease, liver disease, insomnia, peptic ulcer, previous neoplasms non-colorectal cancer, inflammatory bowel disease, and colorectal polyps. The second set of covariates was conditions clearly defined as indications of anti-inflammatory drugs: osteoporosis fracture, osteoarthritis, and spondyloarthropathy.

Statistical analysis

Unconditional logistic regression models were used for multivariate analyses and to calculate ORs and 95% confidence intervals (CI). We compared the association of "no use" versus "any use of drug" and assessed associations of dose (DDD) and duration of use. Trend test *P* values were derived from likelihood ratio tests of ordinal variables coded with integers for consecutive categories and considering them as numerical in the logistic regression model. Subgroup analyses were performed according to gender, age, BMI ($\leq$25 vs. >25 kg/m^2), NSAIDs use, and cancer location (colon or rectum). To impute missing data for BMI, a linear model according to age, gender, and outcome status was used (74% had complete data). All models were adjusted, in addition to the matching variables (age, gender, and study area), by two scores, one adjustment score built on potential confounders for colorectal cancer and a propensity score to adjust for the indications of NSAIDs.

We built an adjustment score to minimize bias related to differences between cases and controls potentially related to NSAID consumption. This score was derived as the individual prediction of a logistic regression model using case–control status as response and age, gender, socioeconomic status (MEDEA), health care region, year of inclusion, BMI, smoking, alcohol and comorbidities unrelated to NSAID use as covariates. This score was efficient to render all individual potential confounders nonsignificantly associated to colorectal cancer. The estimates of drug exposures were similar to those obtained with the complex models including each variable individually. To minimize the possible confounding by indication we used a propensity score approach (32). The propensity score was derived from a logistic regression model of the exposure to either chondroitin sulfate or glucosamine (ever/never) according to all the potential indications of anti-inflammatory drugs. There was no need to trim the data as cases and controls had a similar range of propensity and adjustment scores. All risk models for colorectal cancer included both adjustment scores as continuous variables. Statistical analysis was carried out using R statistical software (R Foundation for Statistical Computing).

Results

Baseline characteristics

A total of 25,811 colorectal cancer cases were included and matched by gender, age at time of index date ($\pm$ 5 years), and health care region to 129,117 controls.

The most prevalent class of medication used was chondroitin sulfate (n = 13,878, 9.0%) followed by glucosamine (n = 11,374, 7.3%). The median estimated cumulative dose of chondroitin sulfate and glucosamine use per day was 120 DDD for chondroitin sulfate (IQR: 60–330) and 90 DDD for glucosamine (IQR: 40–270) for both colorectal cancer case patients and control participants. Median duration of use was 6 months (IQR: 1–30) for chondroitin sulfate and 4 months (IQR: 1-30) for glucosamine.

Patient characteristics associated with use of each drug class can be found in **Table 1**. Advanced age, female gender, social deprivation, obesity, not consuming tobacco or alcohol, and NSAIDs prescription were associated to both chondroitin sulfate and glucosamine use. Also, chondroitin sulfate and glucosamine users were more likely to have comorbidities (see Supplementary Table S1A and S1B).

Chondroitin sulfate and glucosamine consumption and colorectal cancer risk

Ever use of chondroitin sulfate was associated with a nonsignificant 4% reduced risk of colorectal cancer (OR: 0.96; 95% CI, 0.91–1.01). Analyses taking into account the type of exposure are shown in **Table 2A**. This association was stronger for past exposures (OR for exposure more than 3 years before the index date: 0.92; 95% CI, 0.86–0.98). There was a slight dose–response trend with longer duration of use (OR for >36 months: 0.92; 95% CI, 0.83–1.02) and cumulative DDDs of exposure (OR for >240 DDDs: 0.91; 95% CI, 0.84–0.99). In the stratified analysis by NSAIDs (**Table 2A**), we observed a paradoxical opposite association: users of only chondroitin sulfate had a higher risk of colorectal cancer (OR: 1.16; 95% CI, 1.00–1.34), while among NSAID users, chondroitin sulfate was negatively associated with colorectal cancer risk (OR: 0.93; 95% CI, 0.88–0.98, $P_{\text{interaction}} = 0.0037$).

Ever use of glucosamine was associated with a significant 8% reduced risk of chondroitin sulfate (OR: 0.92; 95% CI, 0.87–0.97). This risk was similar for recent or past exposures. There was a dose–response relationship for duration, and more evident for cumulative DDDs (OR for >240 DDDs: 0.85; 95% CI, 0.77–0.94; **Table 2B**). In the stratified analysis by NSAID use, we did not observe an effect modification ($P_{\text{interaction}} = 0.52$).

As chondroitin sulfate and glucosamine are often used in combination, we also analysed the protective association of the combination either under concomitant use or not (**Table 3**). The stratified analysis showed that there was an increased protective association with concurrent use of chondroitin sulfate and glucosamine (OR: 0.83; 95% CI, 0.70–0.98) suggesting a possible synergistic effect.

Associations were also examined after stratifying by age, gender, BMI, and tumor location (**Table 2A** and **B**). The protective association of chondroitin sulfate was stronger among men (OR: 0.90; 95% CI, 0.84–0.97) than women (OR: 0.98; 95% CI, 0.92–1.02; $P_{\text{interaction}} = 0.053$), but no effect modification was observed in glucosamine users ($P = 0.15$). There were no differences when analyzing age or BMI. The protective association was slightly higher in rectum than colon cancers among chondroitin sulfate and glucosamine users, although the interaction was not significant (Supplementary Table S2).

NSAID consumption and colorectal cancer risk

The protective association of NSAIDs against colorectal cancer is shown in **Table 4**. Other than acetylsalicylic acid, the NSAID most used was ibuprofen (60%), but only 17% of the subjects used more than 100 DDDs. Using this filter for all drugs, the second most frequently used NSAID was diclofenac (6.7%). Ever use on any NSAID, with a frequency of 35% among controls, had a protective association with colorectal cancer, with an 11% risk reduction (OR: 0.89; 95% CI, 0.87–0.92). This protective association was higher with longer exposure (OR for >10 years: 0.79; 95% CI, 0.76–0.84) and with higher cumulative dose (OR for >1,800 DDD: 0.80; 95% CI, 0.77–0.84; Supplementary

Table 1. Characteristics of the study according to chondroitin sulfate or glucosamine use (controls only).

Characteristics	Chondroitin sulfate			Glucosamine		
	CS nonusers *n* (%)	CS users *n* (%)	Crude OR (95% CI)	G nonusers *n* (%)	G users *n* (%)	Crude OR (95% CI)
Age						
18–60 years	25,079 (21.4)	1,389 (11.9)	1	25,727 (21.5)	741 (7.7)	1
60–70 years	29,654 (25.2)	3,415 (29.3)	2.08 (1.95–2.22)	30,610 (25.6)	2,459 (25.6)	2.79 (2.56–3.03)
70–80 years	34,530 (29.4)	4,239 (36.4)	2.22 (2.08–2.36)	35,096 (29.4)	3,673 (38.3)	3.63 (3.35–3.94)
80–95 years	28,202 (24.0)	2,609 (22.4)	1.67 (1.56–1.79)	28,084 (23.5)	2,727 (28.4)	3.37 (3.10–3.66)
Sex						
Male	71,141 (60.6)	5,528 (47.4)	1	72,230 (60.4)	4,439 (46.2)	1
Female	46,324 (39.4)	6,124 (52.6)	1.70 (1.64–1.77)	47,287 (39.6)	5,161 (53.8)	1.78 (1.70–1.85)
Deprivation Index Score MEDEA[a]						
Urban Q1 (least deprived)	18,977 (17.4)	2,358 (21.5)	1	19,706 (17.7)	1,629 (18.1)	1
Urban Q2	17,718 (16.2)	1,966 (17.9)	0.89 (0.84–0.95)	18,005 (16.2)	1,679 (18.7)	1.13 (1.05–1.21)
Urban Q3	17,453 (16.0)	1,797 (16.4)	0.83 (0.78–0.88)	17,703 (15.9)	1,547 (17.2)	1.06 (0.98–1.14)
Urban Q4	17,019 (15.6)	1,662 (15.2)	0.79 (0.74–0.84)	17,296 (15.6)	1,385 (15.4)	0.97 (0.90–1.04)
Urban Q5 (most deprived)	14,779 (13.5)	1,228 (11.2)	0.67 (0.62–0.72)	14,904 (13.4)	1,103 (12.3)	0.90 (0.83–0.97)
Rural	23,194 (21.3)	1,953 (17.8)	0.68 (0.64–0.72)	23,502 (21.2)	1,645 (18.3)	0.85 (0.79–0.91)
Body mass index						
≤25 kg/m^2	19,260 (16.4)	1,726 (14.8)	1	19,625 (16.4)	1,361 (14.2)	1
25.1-30.0 kg/m^2	71,313 (60.7)	6,280 (53.9)	0.98 (0.93–1.04)	72,516 (60.7)	5,077 (52.9)	1.01 (0.95–1.07)
>30 kg/m^2	26,892 (22.9)	3,646 (31.3)	1.51 (1.42–1.61)	27,376 (22.9)	3,162 (32.9)	1.67 (1.56–1.78)
Tobacco[a]						
Nonsmoker	59,444 (60.3)	7,564 (69.0)	1	60,531 (60.2)	6,477 (71.2)	1
Former smoker	22,758 (23.1)	2,335 (21.3)	0.81 (0.77–0.85)	23,233 (23.1)	1,860 (20.4)	0.75 (0.71–0.79)
Current smoker	16,426 (16.7)	1,057 (9.6)	0.51 (0.47–0.54)	16,722 (16.6)	761 (8.4)	0.43 (0.39–0.46)
Alcohol[a]						
None/mild	54,849 (63.5)	6,669 (66.0)	1	55,869 (63.4)	5,649 (67.7)	1
Moderate	29,275 (33.9)	3,259 (32.2)	0.92 (0.88–0.96)	29,959 (34.0)	2,575 (30.8)	0.85 (0.81–0.89)
Severe	2,254 (2.6)	178 (1.8)	0.65 (0.56–0.76)	2,308 (2.6)	124 (1.5)	0.53 (0.44–0.64)
NSAIDs						
Nonusers	77,859 (66.3)	5,484 (47.1)	1	78,953 (66.1)	4,390 (45.7)	1
Users	39,606 (33.7)	6,168 (52.9)	2.21 (2.13–2.3)	40,564 (33.9)	5,210 (54.3)	2.31 (2.22–2.41)

Abbreviations: CS, chondroitin sulfate; G, glucosamine; NSAID, nonsteroidal anti-inflammatory drugs including acetylsalicylic acid.
[a]Variable with missing values.

Table S3). The highest protective association was observed with indomethacin while dexketoprofen was the only one with no protective association (**Table 4**).

Although all the previous reported associations were adjusted for NSAID use, we also explored a stratified analysis of the concomitant use of chondroitin sulfate or glucosamine with NSAIDs (**Table 5**). The prevalence of the combination use, simultaneously or not, was around 2.4%. The exclusive consumption of chondroitin sulfate without NSAIDs was not associated to colorectal cancer or when use was not concomitant with NSAID. In that case, chondroitin sulfate use was more frequent among cases than controls (OR: 1.10; 95% CI, 0.90–1.33). Similarly, there was a lack of protective association for glucosamine in the small subgroup that consumed it without NSAIDs (OR: 0.96; 95% CI, 0.87–1.07). The use of chondroitin sulfate or glucosamine simultaneously to NSAID showed, however, an increased protective association compared with the use of either drug alone (OR: 0.80; 95% CI, 0.72–0.88). Both the combination of NSAID + chondroitin sulfate or NSAID + glucosamine had a similar OR = 0.82 (95% CI, 0.76–0.88).

Discussion

In this medical-record population-based case–control study, we observed a reduced risk of colorectal cancer associated to the use of chondroitin sulfate and glucosamine in the adjusted analysis. However, in the stratified analysis with NSAIDs this association was only observed for glucosamine alone or when each drug was used with a concomitant NSAID. The associations showed a dose–response relationship, both regarding duration of use and cumulative DDDs. Although the median duration was short, 6 months, subjects using glucosamine more than 12 months or 90 cumulative DDDs (about 4% of the population) already had a reduced risk of colorectal cancer. The trend regarding duration was not so evident for chondroitin sulfate, but cumulative DDD >240 also were associated with decreased risk.

A protective association of these drugs was initially reported by Satia and colleagues (11) in an exploratory analysis within the VITamins And Lifestyle (VITAL) study. The use of glucosamine and chondroitin sulfate supplements were associated with reduced risk of colorectal cancer after 5 years of follow-up (12). Subsequently, Kantor and colleagues also found a reduced risk of colorectal cancer in two prospective cohorts in North America (13, 15). Our group, analyzing the MCC-Spain case–control study, found an association of chondroitin sulfate and glucosamine that was no longer significant when adjusted for NSAID use (14). In that study, the protective association of chondroitin sulfate and glucosamine was restricted to patients with concurrent non-NSAID use, but was null among nonusers of NSAIDs, although the estimate was based on very small numbers. Here, we confirm with a very large sample size similar results, and have to

Table 2A. Chondroitin sulfate and colorectal cancer risk.

		Controls *n* (%)	CRC cases *n* (%)	OR[a] (95% CI)	P_{trend}[b]
Ever use	CS nonuser	117,465 (91.0)	23,585 (91.4)	1	0.10
	CS user	11,652 (9.0)	2,226 (8.6)	0.96 (0.91–1.01)	
Time since last use	Nonuser	117,465 (91.0)	23,585 (91.4)	1	0.030
	Current exposure (<36 months)	5,511 (4.3)	1,103 (4.3)	1.01 (0.94–1.08)	
	Old exposure (≥36 months)	6,141 (4.8)	1,123 (4.4)	0.92 (0.86–0.98)	
Duration	Nonuser	117,465 (91.0)	23,585 (91.4)	1	0.049
	<12 months	6,752 (5.2)	1,327 (5.1)	0.98 (0.92–1.04)	
	12–36 months	2,372 (1.8)	440 (1.7)	0.94 (0.85–1.04)	
	≥36 months	2,528 (2.0)	459 (1.8)	0.92 (0.83–1.02)	
Cumulative dose	Nonuser	117,465 (91.0)	23,585 (91.4)	1	0.052
	<90 DDD	4,199 (3.3)	825 (3.2)	0.98 (0.90–1.05)	
	90–240 DDD	3,659 (2.8)	717 (2.8)	0.99 (0.91–1.07)	
	>240 DDD	3,794 (2.9)	684 (2.7)	0.91 (0.84–0.99)	
Stratified analysis[c]				**OR (95% CI)**	$P_{interaction}$[d]
Age (years)	≤71	5,666 (8.4)	1,044 (7.9)	0.92 (0.85–0.98)	0.17
	>71	5,986 (9.7)	1,182 (9.4)	0.98 (0.91–1.05)	
Sex	Male	5,528 (7.2)	1,012 (6.6)	0.90 (0.84–0.97)	0.053
	Female	6,124 (11.7)	1,214 (11.6)	0.98 (0.92–1.05)	
Body mass index[e]	≤25 kg/m^2	1,726 (8.2)	327 (7.1)	0.90 (0.79–1.02)	0.88
	>25 kg/m^2	7,994 (10.9)	1,538 (10.1)	0.95 (0.90–1.01)	
NSAID use	Nonuser	981 (2.4)	228 (3.0)	1.16 (1.00–1.34)	0.0037
	User	10,671 (12.0)	1,998 (11.0)	0.93 (0.88–0.98)	

Abbreviations: CRC, colorectal cancer; CS, chondroitin sulfate; NSAID, nonsteroidal anti-inflammatory drugs including acetylsalicylic acid.
[a]Adjusted for age, sex, socioeconomic status, region, year, body mass index, smoking, alcohol, Charlson comorbidity index, NSAID use, glucosamine use, and the propensity score for chondroitin sulfate or glucosamine use.
[b]All variables (except ever use) are considered as ordinal.
[c]OR for chondroitin sulfate, stratified for groups and adjusted for potential confounders.
[d]$P_{interaction}$ between chondroitin sulfate and stratification factor.
[e]Subjects with missing values were excluded.

Table 2B. Glucosamine and colorectal cancer risk.

		Controls *n* (%)	CRC cases *n* (%)	OR[a] (95% CI)	P_{trend}[b]
Ever use	G nonuser	119,517 (92.6)	24,037 (93.1)	1	0.0088
	G user	9,600 (7.4)	1,774 (6.9)	0.92 (0.87–0.97)	
Time since last use	Nonuser	119,517 (92.6)	24,037 (93.1)	1	0.0031
	Current exposure (<36 months)	2,939 (2.3)	541 (2.1)	0.92 (0.84–1.01)	
	Old exposure (≥36 months)	6,661 (5.2)	1,233 (4.8)	0.92 (0.86–0.98)	
Duration	Nonuser	119,517 (92.6)	24,037 (93.1)	1	0.0011
	<12 months	5,735 (4.4)	1,106 (4.3)	0.95 (0.89–1.02)	
	12–36 months	1,769 (1.4)	287 (1.1)	0.81 (0.71–0.92)	
	≥36 months	2,096 (1.6)	381 (1.5)	0.91 (0.82–1.02)	
Cumulative dose	Nonuser	119,517 (92.6)	24,037 (93.1)	1	0.0001
	<90 DDD	4,247 (3.3)	851 (3.3)	0.99 (0.92–1.07)	
	90–240 DDD	2,627 (2.0)	462 (1.8)	0.87 (0.79–0.97)	
	>240 DDD	2,726 (2.1)	461 (1.8)	0.85 (0.77–0.94)	
Stratified analysis[c]				**OR (95% CI)**	$P_{interaction}$[d]
Age (years)	≤71	3,905 (5.8)	701 (5.3)	0.90 (0.82–0.97)	0.95
	>71	5,695 (9.2)	1,073 (8.5)	0.91 (0.85–0.98)	
Sex	Male	4,439 (5.8)	790 (5.2)	0.87 (0.81–0.95)	0.15
	Female	5,161 (9.8)	984 (9.4)	0.92 (0.86–1.00)	
Body mass index[e]	≤25 kg/m^2	1,361 (6.5)	247 (5.4)	0.86 (0.74–0.99)	0.83
	>25 kg/m^2	6,765 (9.3)	1,278 (8.4)	0.93 (0.87–0.99)	
NSAID use	Nonuser	787 (2.0)	153 (2.0)	0.91 (0.76–1.08)	0.52
	User	8,813 (9.9)	1,621 (8.9)	0.91 (0.86–0.96)	

Abbreviations: CRC, colorectal cancer; G, glucosamine; NSAID, nonsteroidal anti-inflammatory drugs including acetylsalicylic acid.
[a]Adjusted for age, sex, socioeconomic status, region, year, body mass index, smoking, alcohol, Charlson comorbidity index, NSAID use, chondroitin sulfate use, and the propensity score for chondroitin sulfate or glucosamine use.
[b]All variables (except ever use) are considered as ordinal.
[c]OR for glucosamine, stratified for groups and adjusted for potential confounders.
[d]$P_{interaction}$ between glucosamine and stratification factor.
[e]Subjects with missing values were excluded.

Table 3. Simultaneous use of chondroitin sulfate and glucosamine and colorectal cancer risk.

	Controls *n* (%)	CRC cases *n* (%)	OR[a] (95% CI)	*P*[b]
Nonuser	10,978 (86.0)	22,345 (86.7)	1	0.0025
Only G user	6,358 (4.9)	1,214 (4.7)	0.94 (0.88–1.00)	
Only CS user	8,539 (6.6)	1,692 (6.6)	0.97 (0.92–1.03)	
CS and G user not simultaneously	2,129 (1.7)	372 (1.4)	0.86 (0.77–0.96)	
CS and G user simultaneously	984 (0.8)	162 (0.6)	0.83 (0.70–0.98)	

Abbreviations: CRC, colorectal cancer; CS, chondroitin sulfate; G, glucosamine.
[a]Adjusted for age, sex, socioeconomic status, region, year, body mass index, smoking, alcohol, Charlson comorbidity index, nonsteroidal anti-inflammatory drugs, and the propensity score for chondroitin sulfate or glucosamine use.
[b]*P* value for test of heterogeneity.

conclude that the protective association of chondroitin sulfate and glucosamine require simultaneous use of NSAIDs. Interestingly, among subjects consuming that combination, a synergistic effect is observed, and the reduction of colorectal cancer risk is enhanced over that of NSAIDs alone.

Unlike other countries, we could examine the use of chondroitin sulfate and glucosamine alone, which was important as we observed little overlap in chondroitin sulfate and glucosamine exposures. Nevertheless, due to the fact that these supplements are commonly available together (at least in some countries), we have examined the joint association between glucosamine and chondroitin sulfate to compare the results with existing literature. Thus, we have observed a higher protective association of the combination, either under concomitant use or not, suggesting a possible synergistic effect.

We have also analysed the possible effect modification by age, gender, or BMI. Previous studies (11, 12, 15) had controversial results of the association of chondroitin sulfate and glucosamine with colorectal cancer according to BMI. Now, we have not found a differential association regarding these variables as Kantor and colleagues (15) did.

The mechanism through which chondroitin sulfate and glucosamine may reduce the risk of colorectal cancer has been related to their anti-inflammatory effect (33–35). *In vitro* and animal studies suggested that the protective effect might be mediated through reduction in inflammation by the suppression of the NFκβ pathway (12, 13, 36–39), which has anticarcinogenic potential (16). The promoter of *COX-2* gene has binding sites for *NFκβ*, which may explain an interaction between these pathways (40). This is consistent with our results, which indicate that the possible protective effects of chondroitin sulfate and glucosamine are dependent on the simultaneous use of NSAIDs (**Table 5**). We hypothesize that the *NFκβ* inhibition that may be induced by chondroitin sulfate and glucosamine is not sufficient to inhibit inflammation and cellular proliferation in the colon, but requires the blockade of an NSAID. However, the combination of chondroitin sulfate or glucosamine with an NSAID exerts a synergistic effect, seen as a larger reduced risk of colorectal cancer than with the NSAID alone. We cannot explain why chondroitin sulfate alone, without an NSAID, was associated with an increased risk of colorectal cancer in this study. We believe it may be a chance finding or related to residual confounding. This association was only observed for

Table 4. NSAID consumption and colorectal cancer risk.

		Controls *n* (%)	CRC cases *n* (%)	OR[a] (95% CI)	*P*
Acetylsalicylic acid	Nonuser	102,268 (79.2)	20,471 (79.3)	1	0.00011
	User	26,849 (20.8)	5,340 (20.7)	0.92 (0.89–0.95)	
Aceclofenac	Nonuser	126,745 (98.2)	25,424 (98.5)	1	0.00011
	User	2,372 (1.8)	387 (1.5)	0.81 (0.73–0.90)	
Dexketoprofen	Nonuser	128,081 (99.2)	25,628 (99.3)	1	0.11
	User	1,036 (0.8)	183 (0.7)	0.88 (0.75–1.03)	
Diclofenac	Nonuser	120,410 (93.3)	24,318 (94.2)	1	<0.0001
	User	8,707 (6.7)	1,493 (5.8)	0.83 (0.78–0.88)	
Ibuprofen	Nonuser	106,564 (82.5)	21,572 (83.6)	1	0.000013
	User	22,553 (17.5)	4,239 (16.4)	0.90 (0.87–0.93)	
Indomethacin	Nonuser	128,199 (99.3)	25,673 (99.5)	1	0.00050
	User	918 (0.7)	138 (0.5)	0.73 (0.61–0.88)	
Naproxen	Nonuser	124,740 (96.6)	25,002 (96.9)	1	0.010
	User	4,377 (3.4)	809 (3.1)	0.91 (0.84–0.98)	
Celecoxib	Nonuser	127,324 (98.6)	25,515 (98.9)	1	0.0017
	User	1,793 (1.4)	296 (1.1)	0.82 (0.73–0.93)	
Any NSAID	Nonuser	83,343 (64.5)	16,846 (65.3)	1	<0.0001
	User	45,774 (35.5)	8,965 (34.7)	0.89 (0.87–0.92)	

Note: Nonuser defined as consuming ≤100 DDD.
Abbreviation: NSAID, nonsteroidal anti-inflammatory drugs including acetylsalicylic acid.
[a]Adjusted for age, sex, socioeconomic status, region, year, body mass index, smoking, alcohol, and Charlson comorbidity index.

Table 5. Chondroitin sulfate or glucosamine association to risk of colorectal cancer according to NSAID use.

	Control *n* (%)	Case *n* (%)	(95% CI) Adjusted OR[a]	*P*
Chondroitin and NSAIDs				
CS nonuser - NSAID nonuser	77,859 (60.3)	15,726 (60.9)	1	<0.0001
CS user - NSAID nonuser	5,484 (4.2)	1,120 (4.3)	0.99 (0.92–1.06)	
CS nonuser - NSAID user	39,606 (30.7)	7,859 (30.4)	0.91 (0.88–0.93)	
CS user - NSAID user not simultaneously	546 (0.4)	128 (0.5)	1.10 (0.90–1.33)	
CS user - NSAID user simultaneously	5,622 (4.4)	978 (3.8)	0.82 (0.76–0.88)	
Glucosamine and NSAIDs				
G nonuser - NSAID nonuser	78,896 (61.1)	16,019 (62.1)	1	<0.0001
G user - NSAID nonuser	2,279 (1.8)	463 (1.8)	0.96 (0.87–1.07)	
G nonuser - NSAID user	40,444 (31.3)	7,994 (31.0)	0.90 (0.87–0.92)	
G user - NSAID user not simultaneously	582 (0.5)	126 (0.5)	1.00 (0.82–1.22)	
G user - NSAID user simultaneously	6,916 (5.4)	1,209 (4.7)	0.82 (0.77–0.87)	
Chondroitin and/or glucosamine and NSAIDs				
CS and/or G nonuser - NSAID nonuser	81,989 (63.5)	16,604 (64.3)	1	<0.0001
CS and/or G user - NSAID nonuser	168 (0.1)	37 (0.1)	1.06 (0.74–1.51)	
CS and/or G nonuser - NSAID user	44,015 (34.1)	8,673 (33.6)	0.90 (0.87–0.92)	
CS and/or G user - NSAID user not simultaneously	353 (0.3)	56 (0.2)	0.75 (0.57–1.00)	
CS and/or G user - NSAID user simultaneously	2,592 (2.0)	441 (1.7)	0.80 (0.72–0.88)	

Abbreviations: CS, chondroitin sulfate; G, glucosamine; NSAID, nonsteroidal anti-inflammatory drugs including acetylsalicylic acid.
[a]Adjusted for age, sex, socioeconomic status, region, year, body mass index, smoking, alcohol, Charlson comorbidity index. Also, adjusted by chondroitin sulfate and glucosamine use depending on the analyses.

chondroitin sulfate, not for glucosamine, although glucosamine alone or when used without a concomitant NSAID did not decrease the risk of colorectal cancer.

Our study has several strengths. It is substantially larger and has greater statistical power than our previous study (14). Our study had the advantage of using information extracted from a population-based primary health care database that had virtually complete data on drug dispensations and cancer diagnoses. Thus, the possibility of selection and information bias was minimized. Moreover, we included a high number of colorectal cancer cases ($n = 25{,}811$) in a 6-year period (2010–2015) which was consistent with those expected on the basis of the incidence data of Catalonia registries (41). But this study also has several limitations. First, although we adjusted for multiple potential confounders in the statistical analysis, there was no information on some variables associated with colorectal cancer such as family history of colorectal cancer, dietary habits, physical activity use, or history of colonoscopy or polypectomy. Some potential confounding variables like BMI had many missing values that required imputation and others like tobacco and alcohol use may have been underreported, although SIDIAP data has generally been validated (28). Second, the use of pharmacy records that correspond to dispensing data rather than usage data might have resulted in an overestimation of drug use. However, there is no reason to assume that this would be different for cases and controls and, in contrast, recall bias was minimized. The reported prevalence of use in the United States and Spain is around 13% (10, 13), a little higher than what we observed. In Spain, all the drugs studied are subsidized, and patients aged >65 years get them free of charge, which might minimize the over-the-counter use of chondroitin sulfate and glucosamine. Prevalence of NSAID use might be more underestimated as they are more often purchased over the counter. We used some restrictions to minimize potential biases: first, exposures during the year before the index date were ignored, to avoid differential use just before disease diagnosis; also, NSAID exposures other than chondroitin sulfate and glucosamine smaller than 100 DDDs were ignored, to avoid occasional use of these drugs, often related to their use as analgesics.

In conclusion, this study has observed that chondroitin sulfate and specially glucosamine are associated with a reduced risk of colorectal cancer with a dose–response effect, but when stratified by NSAID use, neither chondroitin sulfate nor glucosamine show an independent association with colorectal cancer risk. However, these drugs may have a synergistic beneficial effect among NSAID users.

Disclosure of Potential Conflicts of Interest

V. Moreno is a consultant for Ferrer S.A., reports receiving commercial research grants from Universal DX and Bioiberica S.A.U., and has ownership interest (including patents) in Aniling. No potential conflicts of interest were disclosed by the other authors.

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