Regular Glucosamine Use May Have Different Roles in the Risk of Site-Specific Cancers: Findings from a Large Prospective Cohort

Fu-Xiao Li[1], Hou-Yu Zhao[2], Teng-Fei Lin[1], Yi-Wen Jiang[1], Di Liu[1], Chang Wei[1], Zi-Yi Zhao[1], Zu-Yao Yang[3], Feng Sha[1], Zhi-Rong Yang[1,4], and Jin-Ling Tang[1,5]

ABSTRACT

Background: Previous studies indicated that glucosamine supplements may have a general anticancer effect. This study aimed to assess whether the potential effect differs across different types of cancers in a large prospective cohort study.

Methods: All participants from the UK Biobank who were free of cancers and had complete information on glucosamine use at baseline were included and followed up from 2006 until 2021. Cox proportional hazards models were used to assess the associations between regular glucosamine use and different site-specific cancers. Subgroup analyses were performed to explore potential interactions. Several sensitivity analyses were conducted to assess the robustness of the main findings.

Results: A total of 450,207 eligible participants (mean age: 56.2 years; females: 53.3%) were included, of whom 84,895 (18.9%) reported regular glucosamine use at baseline. During a median of 12.5 years follow-up, glucosamine use was significantly associated with an increased risk of overall cancer [HR, 1.04; 95% confidence interval (CI), 1.01–1.06], skin cancer (HR, 1.11; 95% CI, 1.07–1.15), and prostate cancer (HR, 1.07; 95% CI, 1.01–1.13), and with a reduced risk of lung cancer (HR, 0.88; 95% CI, 0.79–0.97) after adjusting for potential confounders. Statistical interaction was observed for gender, age, and education for the association of glucosamine use with overall cancer risk (all $P_{interaction} < 0.027$). These results remained unchanged in the sensitivity analyses.

Conclusions: Regular glucosamine use was associated with lower risk of lung cancer but higher risk of skin cancer, prostate cancer, and overall cancer.

Impact: The roles of glucosamine use potentially differ in the development of different site-specific cancers.

Introduction

Cancer remains the leading cause of death and poses a huge threat to life expectancy worldwide, with an estimated 19.3 million newly diagnosed cancer cases and almost 10.0 million cancer-related deaths in 2020 (1). As inflammation plays an important role in carcinogenesis and cancer progression, anti-inflammatory drugs are considered a potential intervention for cancer prevention (2–4).

While commonly used for treating osteoarthritis and joint pain (3, 5–8), glucosamine has gained popularity, as a kind of non-vitamin and nonmineral dietary supplement with anti-inflammatory properties and low risk of adverse effects, in the United States and most European countries for its potential in the prevention of many inflammation-related diseases including cancer (9–11). However, no randomized controlled trials have evaluated the efficacy of glucosamine in preventing cancers. Current evidence supporting the anticancer benefit was mainly from population-based observational studies, which suggested the associations between glucosamine use and reduced risk of lung cancer and colorectal cancer (12–18). However, given huge heterogeneities in the carcinogenesis of different site-specific cancers, it is unclear whether this potential anticancer effect of glucosamine could apply to other cancer types, especially those that were less studied, such as prostate cancer and skin cancer. In addition, heterogeneities may also exist across previous studies conducted in different populations. Comprehensive investigations examining these associations for various site-specific cancers in the same population are urgently required to inform the proper use of glucosamine in the prevention of different types of cancers.

In this study, we examined the associations between glucosamine use and risk of overall cancer and 19 site-specific cancers of interest based on data from the large-scale nationwide prospective UK Biobank cohort study.

Materials and Methods

Participants and setting

The UK Biobank is a population-based prospective cohort study with over 500,000 participants aged 40 to 69 years enrolled between 2006 and 2010 in the United Kingdom. Detailed information on the UK Biobank has been described elsewhere (19). Baseline characteristics of all participants were recorded from self-reports, interviews, and physical measurements. All participants who had not been diagnosed with cancer before baseline enrollment were included in this study.

[1]Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China. [2]Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China. [3]Division of Epidemiology, JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong, China. [4]Primary Care Unit, Department of Public Health and Primary Care, School of Clinical Medicine, University of Cambridge, Cambridge, UK. [5]Department of Clinical Data Center, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China.

Corresponding Authors: Zhi-Rong Yang, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, 518055, China. E-mail: zr.yang@siat.ac.cn, zy266@medschl.cam.ac.uk; and Feng Sha, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, 1068 Xueyuan Avenue, Shenzhen 518055, China. E-mail: feng.sha@siat.ac.cn

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Exposure assessment

Participants were asked "do you regularly take any of the following" (data-field 6179) at baseline. Each participant could make multiple selections from a list of supplements including glucosamine, fish oil, selenium, iron, zinc, and calcium, or none of the above. Participants indicating regular use of glucosamine supplements were defined as glucosamine users, and otherwise as nonusers. Participants with missing data on this information were excluded from the study.

Outcome ascertainment

Data on incidence of cancers were obtained via linkage to national registries, in which cancer diagnoses were defined according to the International Classification of Disease, 10th Revision (ICD-10; data-field 40006; ref. 20). Outcomes of overall cancer and 19 site-specific cancers of interest (cervical, ovarian, endometrium, other female specific cancers, lung, brain, kidney, breast, prostate, other male specific cancers, malignant melanoma, esophagus, stomach, colorectal, pancreas, hepatobiliary, thyroid, skin, all other cancer) were identified from cancer diagnosis records using predefined ICD-10 codes (Supplementary Table S1). Participants were followed up from baseline enrollment until the onset of study outcomes, death, or the end of follow-up [defined as the date of the last occurrence of death in all included participants (November 10, 2021)], whichever came first.

Covariates ascertainment

In our analysis we adjusted for potential confounders, which were common known risk factors for cancers (21, 22). These factors included sociodemographic (gender, ethnicity, education, and Townsend Deprivation Index), lifestyle factors [smoking status, alcohol consumption, vegetable consumption, processed meat intake, fresh fruit intake, vitamin supplements, mineral supplements, body mass index (BMI), and physical activities], and medical conditions and services [osteoarthritis, rheumatoid arthritis, joint pain, multiple sclerosis, history of screening for bowel cancer or breast cancer, prostate-specific antigen test, aspirin, non-aspirin nonsteroidal anti-inflammatory drug (NSAIDs), hormone-replacement therapy, family history of cancer, and overall health rating]. Details of the measurements and definitions for all the covariates are in Supplementary Table S2.

Main analysis

Baseline characteristics of participants were summarized as mean and standard deviation (SD) for continuous variables and frequency and percentages for categorical variables according to the status of glucosamine use. Given the large sample size included in our study, we assessed the between-group differences in baseline characteristics using standardized mean difference (SMD), which is not as sensitive to sample size as traditional tests. An SMD > 0.1 indicated between-group imbalance of baseline characteristics (23).

Cox proportional hazards models were used to estimate the HRs and 95% confidence intervals (CI) for associations between glucosamine use and risk of overall cancer and different types of site-specific cancers. To adjust for potential effect of age, we used age as the time-scale and stratified by birth cohort (every 10-year interval; ref. 24). The proportional hazards assumption was tested using Schoenfeld residuals and we found no violation of the assumption in this study.

Four models were constructed. The basic model (model 1) adjusted for sociodemographic variables. Model 2 adjusted for sociodemographic variables and lifestyle factors. Model 3 adjusted for sociodemographic variables and medical conditions and services. The full model (model 4) adjusted for all the sociodemographic variables, lifestyle factors, and medical conditions and services. History of specific cancer screening was only adjusted for the corresponding cancer outcome. The main analysis was complete-case analysis. Baseline characteristics for all participants included in the study and those included in the main analysis were described to evaluate selection bias.

Secondary analysis

We conducted subgroup analyses using the fully-adjusted model (model 4) to assess potential interactions by the following factors at baseline: age group (<55/≥55 years old), gender, cancer screening history, smoking status, alcohol consumption, overall health rating, ethnicity, education, regular use of vitamin/mineral/other dietary supplements, regularly use of aspirin, regular use of non-aspirin NSAIDs, and disease history of osteoarthritis. The potential effect modifications were assessed by the statistical significance of the cross-product term of the stratifying covariate and glucosamine use in the full model.

Several sensitivity analyses were performed using the full model to test the robustness of our main results. First, to explore the impact of missing data, we conducted multiple imputation with chained equations (25), with five datasets imputed using cancer outcome, follow-up time, glucosamine use, and all potential confounder covariates as independent variables in the models (26). Second, to explore the influence of reverse causation, we excluded new incident cancer cases diagnosed within 2 years of follow-up. Third, we conducted a competing risk analysis treating death as a competing event for cancers. Fourth, we censored events of certain cancer types (i.e., prostate cancer, skin cancer, and malignant melanoma) for overall cancer incidence in male and female participants to explore whether these kinds of cancers contributed most to the increased risk of overall cancer associated with glucosamine use. Fifth, we adopted pack years, instead of smoking status, as a proxy of smoking to adjust for this confounder.

We used R V.3.6.2 (R Development Core Team) for all analyses and $P < 0.05$ (two-sided) was considered statistically significant.

Ethics statement

UK Biobank has approval from the North West Multi-centre Research Ethics Committee as a Research Tissue Bank approval (reference: 11/NW/0382). All participants provided written informed consent.

Data availability

This study was conducted using the UK biobank resource under Application No.80476. All data in this study are available from the UK biobank (www.ukbiobank.ac.uk) on reasonable request, subject to permission by the UK biobank.

Results

Baseline characteristics

A total of 450,207 eligible participants were included in the study, among whom 418,060 with complete data contributed to the main analysis (**Fig. 1**). Baseline characteristics for the 450,207 participants and 418,060 included in the main analysis were similar (Supplementary Table S3). Among 450,207 participants, 84,895 (18.9%) reported regular glucosamine use at baseline (**Table 1**). Compared with nonusers, glucosamine users were more likely to be older, women, and more exposed to non-aspirin NSAIDs, vitamin supplements, and mineral supplements. They also had larger proportions with a history of prostate-specific antigen (PSA) test and breast cancer screening. Among 450,207 participants, 68,579 (15.2%) were diagnosed with

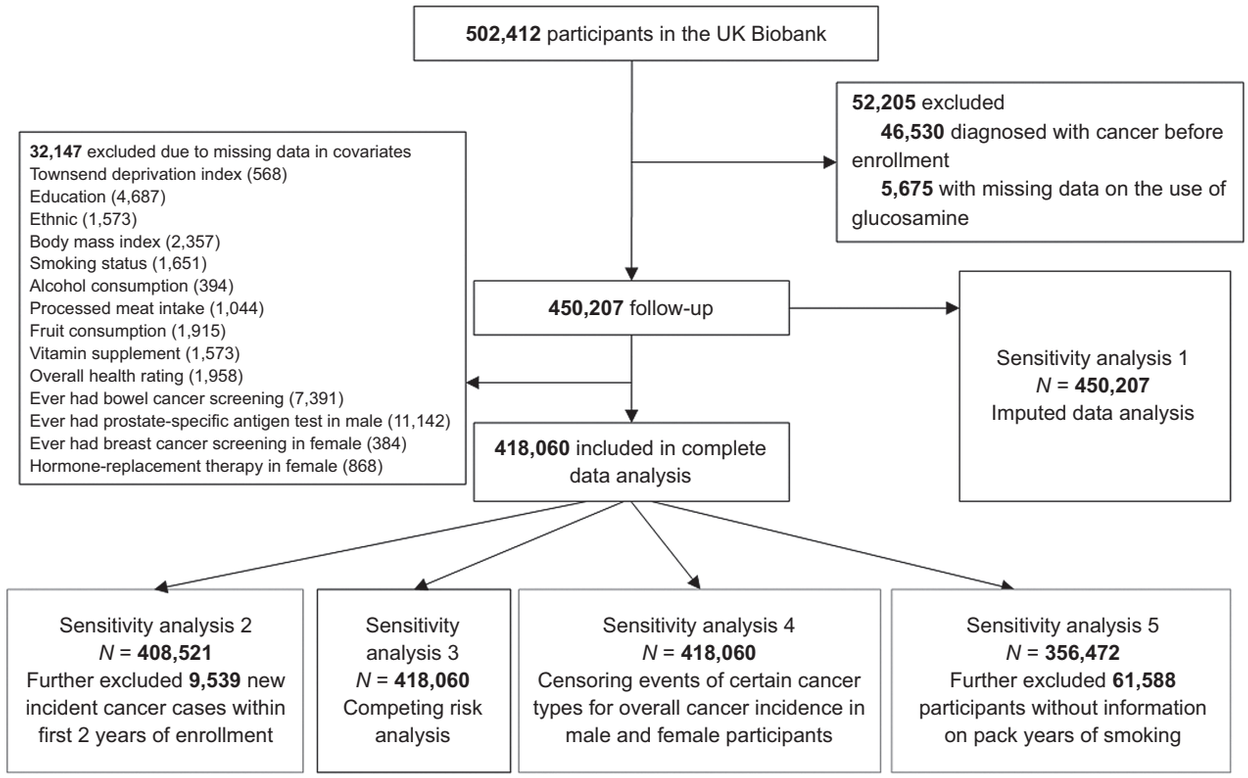

Figure 1.
Flow chart of the UK Biobank participants included in the study. Abbreviation: N, number.

cancer during follow-up and tended to be older and receive cancer screenings (Supplementary Table S4).

Glucosamine use and risk of cancer

In complete-case analysis (**Table 2**), during a median follow-up of 12.4 years [interquartile range (IQR), 11.5–13.3 years] for 80,045 glucosamine users and 12.5 years (IQR, 11.6–13.3 years) for 338,015 nonusers, we identified 63,430 (15.2%) overall cancers. For gender-specific cancers, we identified 9,111 (4.8%) prostate cancers and 475 (3%) other site-specific cancers in males; 447 (0.2%) cervical cancers, 9,068 (4.0%) breast cancers, 843 (0.4%) ovarian cancers, 1,294 (0.6%) endometrium cancers, and 322 (0.1%) other site-specific cancers in females. Besides, we identified 3,136 (0.8%) lung cancers, 846 (0.2%) esophageal cancers, 573 (0.1%) stomach cancers, 5,113 (1.2%) colorectal cancers, 746 (0.2%) hepatobiliary cancers, 1,038 (0.2%) pancreas cancers, 3,467 (0.8%) malignant melanoma cases, 20,668 (4.9%) skin cancers, 1,256 (0.3%) kidney cancers, 359 (0.1%) thyroid cancers, 665 (0.2%) brain cancers, and 8,439 (2.0%) other site-specific cancers.

The magnitudes of association generally decreased as more covariates were progressively adjusted in the model. In the full-adjusted model, glucosamine use was statistically significantly associated with increased risk for overall cancer (HR, 1.04; 95% CI, 1.01–1.06), prostate cancer (HR, 1.07; 95% CI, 1.01–1.13), and skin cancer (HR, 1.11; 95% CI, 1.07–1.15), but with reduced risk for lung cancer (HR, 0.88; 95% CI, 0.79–0.97). There seemed some evidence of an increased risk for malignant melanoma (HR, 1.07; 95% CI, 0.98–1.17) and a decreased risk for kidney (HR, 0.91; 95% CI, 0.78–1.07) and thyroid (HR, 0.80; 95% CI, 0.60–1.08) cancer although the estimates were not statistically significant.

Sensitivity analysis

For overall cancer, lung cancer, skin cancer, and prostate cancer, the statistically significant associations in the main analysis did not change appreciably in all predefined sensitivity analyses (**Table 3**). After censoring prostate cancer and malignant melanoma in male participants or malignant melanoma in female participants (Supplementary Table S5), the associations between glucosamine use and risk of overall cancer incidence did not change appreciably, but disappeared when censoring skin cancer in both groups.

Subgroup analysis

The positive association between glucosamine use and overall cancer risk was modified by gender ($P < 0.0001$), age ($P = 0.016$), and education ($P = 0.027$; **Fig. 2**). For site-specific cancers, age, smoking status, cancer screening experience, and aspirin use showed statistical interactions in certain cancer outcomes, with all P values for interaction less than 0.049 (**Table 4**). Details of results from subgroup analysis are shown in Supplementary Figs. S1 to S19.

Discussion

To our best knowledge, this was the first population-based study to examine the risk of various site-specific cancers associated with glucosamine use in the same population. We discovered that regular glucosamine use was statistically significantly associated with a 4% higher risk of overall cancer, an 11% higher risk of skin cancer, and a 16% lower risk of lung cancer in all participants; and a 7% higher risk of prostate cancer in male participants. These associations were independent of sociodemographic factors, lifestyle factors, medical

Table 1. Baseline characteristics of all participants included in the study.

Characteristics	Total number (%)	Regular glucosamine use, number (%)		SMD[a]
		No	Yes	
Number of participants	450,207	365,312	84,895	
Mean (SD[b]) baseline age (years)	56.2 (8.1)	55.6 (8.2)	58.8 (7.1)	0.379
Women	240,097 (53.3)	187,815 (51.4)	52,282 (61.6)	0.206
TDI[b], mean (SD)	−1.29 (3.09)	−1.18 (3.15)	−1.78 (2.80)	0.201
Mean (SD) body mass index (kg/m^2)	27.4 (4.8)	27.5 (4.8)	27.4 (4.7)	0.019
Education				
College degree or higher	147,400 (32.7)	119,146 (32.6)	28,254 (33.3)	0.023
No college degree	298,120 (66.2)	242,235 (66.3)	55,885 (65.8)	
Unknown	4,687 (1.1)	3,931 (1.1)	756 (0.9)	
Ethnicity				
White	407,183 (90.5)	329,059 (90.1)	78,124 (92)	0.068
Others	41,451 (9.2)	34,935 (9.6)	6,516 (7.7)	
Unknown	1,573 (0.3)	1,318 (0.3)	255 (0.3)	
Smoking status				
Current smokers	47,549 (10.6)	42,004 (11.5)	5,545 (6.5)	0.189
Previous smokers (quit ≥10 years)	74,378 (16.5)	57,866 (15.8)	16,512 (19.5)	
Previous smokers (quit <10 years)	79,099 (17.6)	63,454 (17.4)	15,645 (18.4)	
Never	247,530 (55)	200,618 (54.9)	46,912 (55.3)	
Unknown	1,651 (0.3)	1,370 (0.4)	281 (0.3)	
Smoking (pack years), mean (SD)	8.2 (15.7)	7.7 (15.1)	10.9 (18.7)	0.093
Alcohol consumption				
Daily	91,437 (20.3)	72,452 (19.8)	18,985 (22.4)	0.115
Three or four times a week	104,400 (23.2)	83,234 (22.8)	21,166 (24.9)	
Once or twice a week	116,338 (25.8)	94,947 (26)	21,391 (25.1)	
One to three times a month	50,151 (11.1)	41,161 (11.3)	8,990 (10.6)	
Special occasions only	51,385 (11.4)	42,414 (11.6)	8,971 (10.6)	
Never	36,102 (8.1)	30,746 (8.4)	5,356 (6.3)	
Unknown	394 (0.1)	358 (0.1)	36 (0.1)	
MET[b], min/week				
<600	213,636 (47.5)	178,036 (48.7)	35,600 (41.9)	0.137
≥600	236,571 (52.5)	187,276 (51.3)	49,295 (58.1)	
Vegetable consumption				
>10	18,341 (4.1)	14,530 (4)	3,811 (4.5)	0.154
6–10	121,176 (26.9)	95,219 (26.1)	25,957 (30.6)	
1–5	295,713 (65.7)	242,057 (66.2)	53,656 (63.2)	
never	14,977 (3.3)	13,506 (3.7)	1,471 (1.7)	
Fruit consumption				
>10	733 (0.2)	602 (0.2)	131 (0.2)	0.187
6–10	11,595 (2.6)	8,934 (2.4)	2,661 (3.1)	
1–5	393,654 (87.4)	316,426 (86.6)	77,228 (91)	
never	42,310 (9.4)	37,616 (10.3)	4,694 (5.5)	
Unknown	1,915 (0.4)	1,734 (0.5)	181 (0.2)	
Processed meat intake				
Once or more daily	3,779 (0.8)	3,319 (0.9)	460 (0.5)	0.136
5–6 times a week	14,399 (3.2)	12,334 (3.4)	2,065 (2.4)	
2–4 times a week	122,550 (27.2)	102,007 (27.9)	20,543 (24.2)	
Once a week	130,850 (29.1)	106,429 (29.1)	24,421 (28.8)	
Less than once a week	135,818 (30.2)	107,014 (29.3)	28,804 (33.9)	
Never	41,767 (9.3)	33,293 (9.1)	8,474 (10)	
Unknown	1,044 (0.2)	916 (0.3)	128 (0.2)	
Aspirin				
Yes	61,686 (13.7)	49,981 (13.7)	11,705 (13.8)	0.003
No	388,521 (86.3)	315,331 (86.3)	73,190 (86.2)	
Non-aspirin NSAIDs[b]				
Yes	74,659 (16.6)	52,779 (14.4)	21,880 (25.8)	0.285
No	375,548 (83.4)	312,533 (85.6)	63,015 (74.2)	
Hormone-replacement therapy in female				
Yes	89,718 (37.4)	63,887 (34.0)	25,831 (49.4)	0.316
No	149,511 (62.3)	123,191 (65.6)	26,230 (50.3)	
Unknown	868 (0.4)	737 (0.4)	131 (0.3)	
Vitamin supplements				

(Continued on the following page)

Table 1. Baseline characteristics of all participants included in the study. (Cont'd)

Characteristics	Total number (%)	Regular glucosamine use, number (%)		SMD[a]
		No	Yes	
Yes	141,899 (31.5)	94,833 (26)	47,066 (55.4)	0.631
No	306,735 (68.1)	269,261 (73.7)	37,474 (44.2)	
Unknown	1,573 (0.4)	1,218 (0.3)	355 (0.4)	
Mineral supplements				
Yes	165,771 (36.8)	107,129 (29.3)	58,642 (69.1)	0.867
No	284,436 (63.2)	258,183 (70.7)	26,253 (30.9)	
Overall health rating				
Excellent	75,636 (16.8)	60,676 (16.6)	14,960 (17.6)	0.142
Good	260,897 (58)	208,772 (57.1)	52,125 (61.4)	
Fair	92,432 (20.5)	77,135 (21.1)	15,297 (18)	
Poor	19,284 (4.3)	16,994 (4.7)	2,290 (2.7)	
Unknown	1,958 (0.4)	1,735 (0.5)	223 (0.3)	
Osteoarthritis				
Yes	14,298 (3.2)	9,886 (2.7)	4,412 (5.2)	0.128
No	435,909 (96.8)	355,426 (97.3)	80,483 (94.8)	
Rheumatoid arthritis				
Yes	8,409 (1.9)	6,628 (1.8)	1,781 (2.1)	0.020
No	441,798 (98.1)	358,684 (98.2)	83,114 (97.9)	
Joint pain				
Yes	12,637 (2.8)	9,649 (2.6)	2,988 (3.5)	0.051
No	437,570 (97.2)	355,663 (97.4)	81,907 (96.5)	
Multiple sclerosis				
Yes	1,862 (0.4)	1,572 (0.4)	290 (0.3)	0.014
No	448,345 (99.6)	363,740 (99.6)	84,605 (99.7)	
Family cancer history				
Yes	155,429 (34.5)	124,553 (34.1)	30,876 (36.4)	0.048
No	294,778 (65.5)	240,759 (65.9)	54,019 (63.6)	
Ever had bowel cancer screening				
Yes	134,914 (30)	104,061 (28.5)	30,853 (36.3)	0.169
No	307,902 (68.4)	254,979 (69.8)	52,923 (62.3)	
Unknown	7,391 (1.6)	6,272 (1.7)	1,119 (1.3)	
Ever had PSA[b] test in male				
Yes	57,444 (27.3)	45,632 (25.7)	11,812 (36.2)	0.229
No	141,524 (67.4)	122,272 (68.9)	19,252 (59)	
Unknown	11,142 (5.3)	9,593 (5.4)	1,549 (4.8)	
Ever had breast cancer screening in female				
Yes	188,423 (78.5)	141,579 (75.4)	46,844 (89.6)	0.381
No	51,290 (21.3)	45,891 (24.4)	5,399 (10.3)	
Unknown	384 (0.2)	345 (0.2)	39 (0.1)	

[a]SMD, standardized mean difference (shown as an absolute value). Participants with missing data were included as the "unknown" group when calculating SMD. An SMD >0.1 indicated a between-group imbalance of baseline characteristics.
[b]Abbreviations: SD, standard deviation; TDI, Townsend Deprivation Index; MET, Metabolic Equivalent Task; NSAIDs, nonsteroidal anti-inflammatory drugs; PSA, prostate-specific antigen.

conditions and services. In addition, the positive association between glucosamine use and overall cancer risk was modified by gender, age, and education. The main conclusions did not change substantially in sensitivity analyses.

Our study suggested that regular glucosamine use may have different roles in the risk of site-specific cancers. Our study provided new evidence on the association of glucosamine use with an increased risk of skin cancer, which may be the main contributor to the increased risk of overall cancer. Although we found an increased risk of prostate cancer was associated with glucosamine supplement, the association was not statistically significant from the VITAL cohort (27). For lung cancer, previous studies also found reduced risk associated with glucosamine use (12, 13). These findings also agreed with the association of glucosamine use with the reduced risk of death from lung cancer (28). For colorectal cancer, previous findings have been inconsistent. Four of seven studies in a latest systematic review reported significantly reduced risk of colorectal cancer incidence associated with glucosamine use, but the other three studies did not find statistical significance as in our analysis (17). In addition, our study suggested possible associations for the increased risk of melanoma and lower risk of kidney and thyroid cancers, although not statistically significant, which should be further investigated. The association for kidney cancer was also in line with lower mortality from kidney cancer associated with glucosamine use (28). Given different risk of site-specific cancers associated with glucosamine use, any evidence on glucosamine use for cancer prevention (13, 17) should be treated with caution in the interim when clinical trials have yet to demonstrate the efficacy of glucosamine against these cancers.

Our study identified some novel statistical interactions for the association between glucosamine use and risk of cancers. The association for overall cancer is statistically stronger in man (HR, 1.06; 95% CI, 1.03–1.10) than in women (HR, 1.04; 95% CI, 1.01–1.07), which might be partially explained by the increased risk for prostate cancer only in male participants as well as the higher risk of skin cancer in

Table 2 Association between regular glucosamine use and risk of cancers.

	Regular glucosamine use						Adjusted hazard ratio (95% confidence interval)			
	No ($N = 338,015$)			Yes ($N = 80,045$)			Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Site of cancer	Number of events (%)	Person-years	Incidence (per 1000 person-years)	Number of events (%)	Person years	Incidence (per 1000 person-years)				
Overall cancer	49,596 (14.7)	3,925,149	12.635	13,834 (17.3)	918,147	15.067	**1.03 (1.01–1.05)****	**1.03 (1.01–1.05)****	**1.04 (1.02–1.06)*****	**1.04 (1.01–1.06)** ***
Prostate (male)	7,264 (4.6)	1,843,831	3.940	1847 (6.2)	343,544	5.376	**1.11 (1.05–1.17)*****	**1.09 (1.03–1.15)****	**1.08 (1.03–1.14)****	**1.07 (1.01–1.13)***
Other male specific	401 (0.3)	1,960,805	0.205	74 (0.2)	368,863	0.201	0.90 (0.70–1.15)	0.82 (0.63–1.06)	0.93 (0.72–1.19)	0.84 (0.64–1.09)
Cervical (female)	373(0.2)	2,242,193	0.166	74 (0.1)	630,931	0.117	1.08 (0.84–1.39)	1.18 (0.90–1.54)	1.08 (0.84–1.40)	1.18 (0.90–1.54)
Breast (female)	6,937 (3.9)	2,068,394	3.354	2131 (4.2)	580,142	3.673	1.04 (0.99–1.09)	1.04 (0.98–1.09)	1.03 (0.98–1.08)	1.03 (0.98–1.09)
Ovarian (female)	648 (0.4)	2,045,160	0.317	195 (0.4)	574,998	0.339	0.94 (0.80–1.10)	0.91 (0.77–1.09)	0.94 (0.80–1.11)	0.91 (0.77–1.09)
Endometrium (female)	962 (0.5)	2,244,076	0.429	332 (0.7)	630,466	0.527	1.07 (0.95–1.22)	1.01 (0.89–1.16)	1.10 (0.97–1.25)	1.03 (0.90–1.18)
Other female specific	233 (0.1)	2,244,369	0.104	89 (0.2)	630,996	0.141	1.18 (0.92–1.52)	1.18 (0.91–1.54)	1.17 (0.91–1.50)	1.17 (0.90–1.53)
Lung	2,615 (0.8)	4,202,895	0.622	521 (0.7)	999,567	0.521	**0.74 (0.67–0.81)** ***	**0.85 (0.77–0.94)** **	**0.77 (0.70–0.85)** ***	**0.88 (0.79–0.97)***
Esophagus	700 (0.2)	3,779,066	0.185	146 (0.2)	898,356	0.163	**0.81 (0.67–0.96)***	0.85 (0.70–1.02)	0.84 (0.70–1.00)	0.87 (0.72–1.05)
Stomach	471 (0.1)	3,841,060	0.123	102 (0.1)	913,081	0.112	0.85 (0.69–1.06)	0.96 (0.76–1.21)	0.89 (0.71–1.10)	0.99 (0.78–1.25)
Colorectal	4,072 (1.2)	3,959,252	1.028	1041 (1.3)	941,037	1.106	0.94 (0.87–1.00)	0.95 (0.88–1.02)	0.95 (0.89–1.02)	0.96 (0.89–1.03)
Hepatobiliary	600 (0.2)	3,753,322	0.160	146 (0.2)	892,010	0.164	0.90 (0.75–1.08)	0.96 (0.79–1.17)	0.95 (0.79–1.14)	1.01 (0.83–1.23)
Pancreas	790 (0.2)	3,853,922	0.205	248 (0.3)	915,380	0.271	1.11 (0.96–1.28)	1.13 (0.97–1.32)	1.11 (0.96–1.28)	1.14 (0.97–1.33)
Malignant melanoma	2,674 (0.8)	4,024,980	0.664	793 (1.0)	952,917	0.832	**1.11 (1.03–1.21)****	1.08 (0.99–1.17)	**1.10 (1.01–1.19)***	1.07 (0.98–1.17)
Skin	15,650 (4.6)	4,112,501	3.805	5018 (6.3)	969,892	5.174	**1.13 (1.10–1.17)*****	**1.11 (1.07–1.15)*****	**1.14 (1.10–1.17)*****	**1.11 (1.07–1.15)*****
Kidney	1,026 (0.3)	3,801,720	0.270	230 (0.3)	903,729	0.255	**0.84 (0.73–0.97)***	0.89 (0.76–1.03)	0.87 (0.75–1.01)	0.91 (0.78–1.07)
Thyroid	297 (0.1)	3,756,325	0.079	62 (0.1)	889,399	0.070	**0.73 (0.55–0.96)***	0.78 (0.58–1.05)	**0.75 (0.57–0.99)***	0.80 (0.60–1.08)
Brain	537 (0.2)	3,714,623	0.145	128 (0.2)	882,834	0.145	0.93 (0.76–1.13)	0.92 (0.75–1.13)	0.92 (0.76–1.13)	0.91 (0.74–1.12)
All other cancers	6,734 (2.0)	3,925,149	1.716	1705 (2.1)	918,147	1.857	0.99 (0.93–1.03)	0.99 (0.94–1.05)	1.00 (0.94–1.05)	1.01 (0.95–1.07)

[a]Adjusted for sociodemographic variables (including gender, ethnicity, education and Townsend Deprivation Index).
[b]Adjusted for sociodemographic variables mentioned above and lifestyle factors (including smoking, alcohol consumption, vegetable consumption, processed meat intake, fresh fruit intake, vitamin supplements, mineral supplements, body mass index, and physical activities).
[c]Adjusted for sociodemographic variables mentioned above as well as medical conditions and services (including diagnosis of osteoarthritis/ rheumatoid arthritis/ joint pain/ multiple sclerosis, history of screening for bowel cancer/ breast cancer/ prostate-specific antigen test, use of aspirin/NSAIDs/Hormone-replacement therapy, family history of cancer, and overall health rating).
[d]Adjusted for all covariates mentioned above, including sociodemographic variables, lifestyle factors, and medical conditions and services.
*$P \leq 0.05$.
**$P \leq 0.01$.
***$P \leq 0.001$.

Table 3 Sensitivity analyses for the association between glucosamine use and risk of cancers.

	Adjusted hazard ratio (95% confidence interval)[a]			
Site of Cancer	**Excluding incident cases within 2 years of enrollment (Number = 408,521)**	**Competing risk analysis (Number = 418,060)**	**Multiple imputation analysis (Number = 450,207)**	**Using pack-years adjusting smoking status (Number = 356,472)**
Overall cancer	**1.03 (1.01–1.06)****	**1.03 (1.01–1.05)****	**1.04 (1.02–1.06)*****	**1.03 (1.01–1.06)****
Prostate (male)	**1.08 (1.02–1.15)***	**1.08 (1.02–1.14)****	**1.06 (1.00–1.12)***	**1.05 (1.01–1.10)***
Other male specific	0.77 (0.57–1.04)	0.84 (0.64–1.09)	0.81 (0.63–1.05)	0.79 (0.58–1.07)
Cervical (female)	1.23 (0.90–1.68)	1.03 (0.98–1.08)	1.14 (0.87–1.49)	1.25 (0.94–1.67)
Breast (female)	1.03 (0.97–1.09)	1.03 (0.98–1.08)	1.04 (0.98–1.09)	1.04 (0.98–1.10)
Ovarian (female)	0.95 (0.78–1.15)	0.91 (0.76–1.08)	0.92 (0.78–1.10)	0.92 (0.77–1.12))
Endometrium (female)	1.00 (0.86–1.16)	1.04 (0.91–1.19)	1.05 (0.92–1.19)	1.03 (0.89–1.19))
Other female specific	1.06 (0.79–1.41)	1.16 (0.89–1.50)	1.15 (0.89–1.50)	1.20 (0.90–1.59)
Lung	**0.89 (0.80–1.00)***	**0.85 (0.77–0.94)****	**0.89 (0.81–0.98)***	**0.87 (0.78–0.97)***
Esophagus	0.81 (0.66–1.00)	0.86 (0.71–1.04)	0.86 (0.74–1.06)	0.87 (0.71–1.08)
Stomach	1.06 (0.83–1.36)	0.97 (0.77–1.22)	1.00 (0.80–1.24)	0.94 (0.73–1.21)
Colorectal	0.97 (0.90–1.05)	0.96 (0.89–1.04)	0.97 (0.91–1.05)	0.98 (0.90–1.06)
Hepatobiliary	1.00 (0.81–1.23)	0.99 (0.82–1.21)	1.03 (0.85–1.24)	0.98 (0.79–1.22)
Pancreas	1.12 (0.95–1.32)	1.13 (0.97–1.33)	**1.17 (1.01–1.36)***	1.18 (0.99–1.39)
Malignant melanoma	1.06 (0.96–1.16)	1.08 (0.99–1.17)	1.07 (0.98–1.16)	1.05 (0.96–1.16)
Skin	**1.11 (1.07–1.15)*****	**1.12 (1.08–1.16)*****	**1.12 (1.08–1.15)*****	**1.12 (1.08–1.16)*****
Kidney	0.88 (0.75–1.05)	0.92 (0.79–1.07)	0.90 (0.78–1.04)	0.90 (0.76–1.07)
Thyroid	0.83 (0.60–1.16)	0.89 (0.66–1.21)	0.81 (0.61–1.07)	0.80 (0.59–1.09)
Brain	0.89 (0.71–1.12)	0.93 (0.76–1.15)	0.91 (0.74–1.11)	0.92 (0.73–1.16)
All other cancer	1.00 (0.94–1.07)	1.00 (0.94–1.06)	1.01 (0.96–1.07)	1.01 (0.95–1.08)

[a]All sensitivity analyses were performed using the full model adjusted for sociodemographic variables (including gender, ethnicity, education and Townsend Deprivation Index), lifestyle factors (including smoking, alcohol consumption, vegetable consumption, processed meat intake, fresh fruit intake, vitamin supplements, mineral supplements, body mass index, and physical activities), and medical conditions and services (including diagnosis of osteoarthritis/rheumatoid arthritis / joint pain / multiple sclerosis, history of screening for bowel cancer / breast cancer / prostate-specific antigen test, use of aspirin/NSAIDs/hormone-replacement therapy, family history of cancer, and overall health rating).

*$P \le 0.05$.

**$P \le 0.01$.

***$P \le 0.001$.

male than in female participants. In addition, as indicated by censoring certain cancer types in the sensitivity analysis (Supplementary table S5), skin cancer seems to be the predominant cause for the elevated overall cancer risk in both genders. We also observed a stronger association of glucosamine use with lower risk of colorectal cancer (HR, 0.90; 95% CI, 0.82–0.99; $P_{\text{interaction}} = 0.023$) in participants with no screening but no significant association in screened participants. This might be explained by detection bias where people taking glucosamine and participating in colorectal cancer screening tend to have colorectal cancer detected early. However, the case for prostate cancer was the opposite, with a higher risk of prostate cancer associated with glucosamine use (HR, 1.14; 95% CI, 1.05–1.23; $P_{\text{interaction}} = 0.007$) among those without screening experience. Whether this opposite finding is more likely to indicate biological differences in carcinogenesis or just reflect confounding derived from health-related behaviors should be further investigated. We also observed glucosamine use was associated with increased risk of breast cancer (HR, 1.23; 95% CI, 1.02–1.50) and reduced risk of lung cancer (HR, 0.69; 95% CI, 0.56–0.84) in current smokers. Besides, glucosamine intake was associated with increased risk of esophageal cancer (HR, 4.00; 95% CI, 1.36–11.82) and colorectal cancer (HR, 1.64; 95% CI, 1.18–2.27) in those with a history of osteoarthritis. All these findings have not been reported in previous studies and need further confirmation. Discrepancies of these potential effect modifiers in different site-specific cancers may serve as another reflection of heterogeneity in the roles of glucosamine use in risk of these cancers.

Existing mechanism explorations for the roles of glucosamine in the development of cancers mainly focused on anticancer benefits while harmful effects were reported rarely. For anticancer benefits, glucosamine showed significant reduction of C-reactive protein concentration (6, 29, 30), and may also play a role in cell proliferation, apoptosis, angiogenesis, migration, and invasion (31). Besides, the antioxidant properties of glucosamine could help scavenge the superoxide and hydroxyl radicals and protect the macromolecules (32). Experimental study observed that glucosamine could mimic a low carbohydrate diet with reduced glycolysis and improve amino acid catabolism (33). However, some biological evidence has also been available to support the possibility of the increased risk we observed in prostate cancer. A recent experimental study reported that glucosamine supplementation could increase the concentration of insulin-like growth factor-I (34), which is considered as a risk factor for prostate cancer (35, 36). No previous studies have reported related evidence in terms of glucosamine supplements and increased risk of skin cancer. The increased risk may be a biological consequence of glucosamine use or could be independent of glucosamine but a convergent process due to health behavior factors, such as exposure to solar ultraviolet radiation (37).

This study provided new evidence on the potential heterogeneity in the roles of glucosamine use in the development of different site-specific cancers by examining their associations in the same population. We used data from a population-based prospective cohort with large sample size, long-term follow-up, and detailed information on covariates. Our study has several limitations. First, exposure

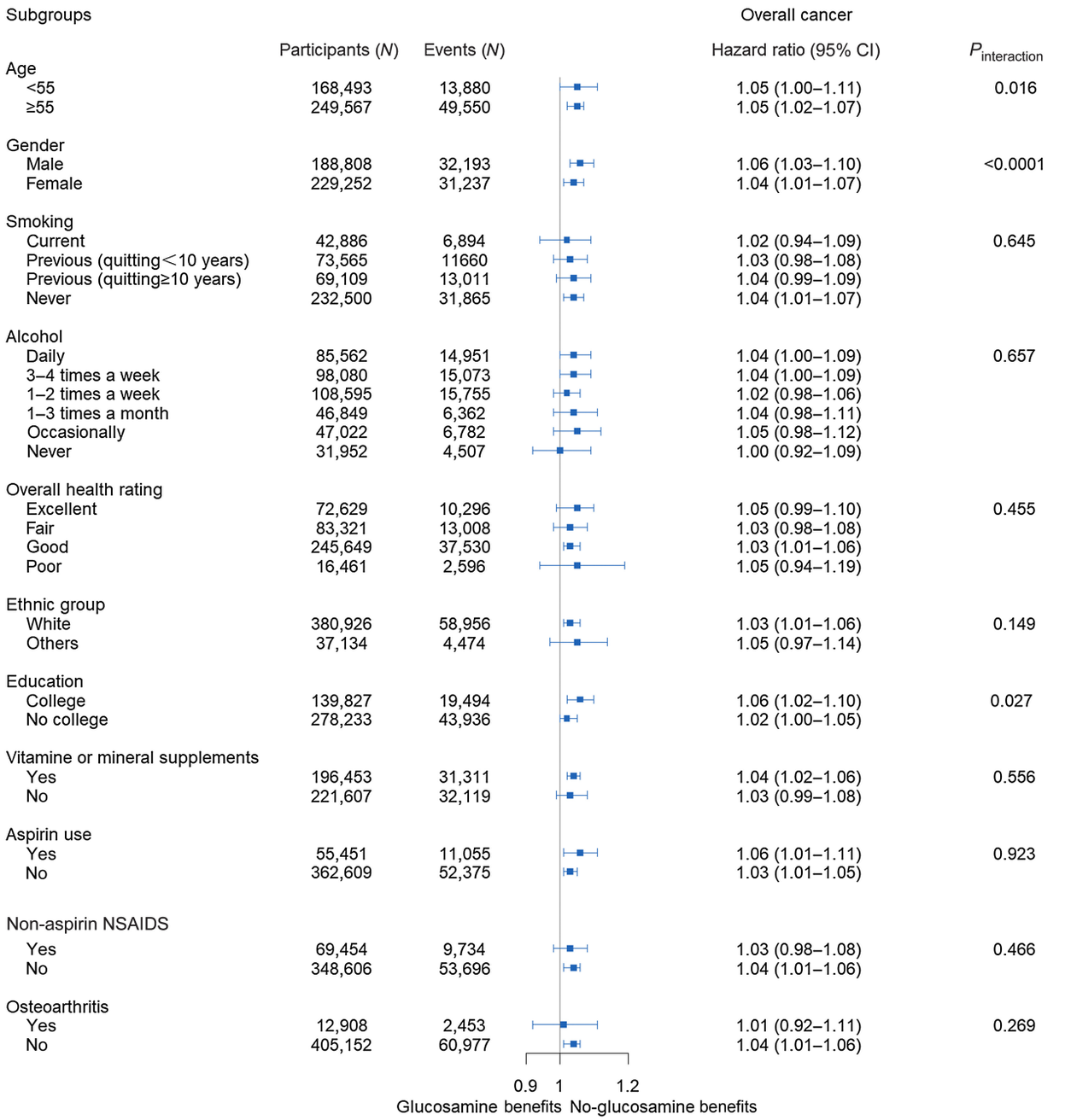

Figure 2.

Subgroup analyses for the association between glucosamine use and risk of overall cancer incidence in participants of the UK Biobank. All HRs were adjusted for sociodemographic variables (including gender, ethnicity, education and Townsend Deprivation Index), lifestyle factors (including smoking, alcohol consumption, vegetable consumption, processed meat intake, fresh fruit intake, vitamin supplements, mineral supplements, body mass index, and physical activities), and medical conditions and services (including diagnosis of osteoarthritis / rheumatoid arthritis / joint pain / multiple sclerosis, use of aspirin/NASAIDS, family history of cancer, and overall health rating). Abbreviation: N, number.

measurement on glucosamine use was based on self-reports without detailed information on dosage, form, frequency, and duration. We only considered baseline exposure without account for the change in glucosamine use over time. We also recognized potential selection bias by including prevalent glucosamine users in the analysis (38). Because of the limited sample size and small number of outcome events among post-baseline users, however, it was not feasible to ascertain the influence of prevalent user bias in our study. Second, participants with cancer diagnoses of multiple sites were identified as incident cases in analyses for different cancer outcomes, and we could not discriminate those who suffered from tumor metastasis from those who actually developed two or more independent cancers. However, there

Table 4 Statistically significant between-group difference in the association between glucosamine use and risk of cancers.

	Stratifying covariates	Number of participants	Number of events	HR (95% CI)[a]	$P_{interaction}$[b]
Overall cancer					
Age	<55	168,493	13,880	1.05 (1.00–1.11)	0.016
	≥55	249,567	49,550	1.05 (1.02–1.07)	
Gender	Male	188,808	32,193	1.06 (1.03–1.10)	<0.0001
	Female	229,252	31,237	1.04 (1.01–1.07)	
Education	College degree or higher	139,827	19,494	1.06 (1.02–1.10)	0.027
	No college degree	278,233	43,936	1.02 (1.00–1.05)	
Lung cancer					
Smoking	Current	42,886	1,238	0.69 (0.56–0.84)	0.004
	Previous (quit <10 years)	73,565	749	0.95 (0.78–1.15)	
	Previous (qui t≥10 years)	69,109	679	0.85 (0.70–1.03)	
	Never	232,500	470	1.17 (0.94–1.47)	
Breast cancer					
Smoking	Current	19,775	778	1.23 (1.02–1.50)	0.026
	Previous (quit <10 years)	39,708	1,685	0.96 (0.85–1.08)	
	Previous (quit ≥10 years)	31,549	1,295	0.95 (0.83–1.09)	
	Never	138,220	5,310	1.06 (0.99–1.13)	
Ethnic group	White	208,274	8,310	1.02 (0.96–1.08)	0.011
	Others	20,978	758	1.17 (0.98–1.40)	
Cervical cancer					
Age	<55	93,651	323	1.44 (1.03–2.01)	0.048
	≥55	135,601	124	0.86 (0.55–1.36)	
Aspirin use	yes	21,730	28	2.92 (1.22–7.02)	0.040
	no	207,522	419	1.08 (0.81–1.44)	
Colorectal cancer					
Ever had bowel cancer screening	yes	125,016	1,846	1.01 (0.90–1.13)	0.023
	no	293,044	3,267	0.90 (0.82–0.99)	
Osteoarthritis	yes	12,908	192	1.64 (1.18–2.27)	0.022
	no	405,152	4,921	0.94 (0.87–1.02)	
Esophageal cancer					
Aspirin use	yes	55,451	187	1.19 (0.82–1.73)	0.013
	no	362,609	659	0.79 (0.63–0.99)	
Osteoarthritis	yes	12,908	18	4.00 (1.36–11.82)	0.016
	no	405,152	828	0.83 (0.68–1.01)	
Malignant melanoma					
Vitamin/mineral supplements	yes	196,453	1,719	1.15 (1.04–1.27)	0.010
	no	221,607	1,748	0.86 (0.71–1.04)	
Other male cancer					
Age	<55	74,842	132	0.50 (0.23–1.10)	0.049
	≥55	113,966	343	0.88 (0.66–1.18)	
Skin cancer					
Gender	male	188,808	10,981	1.13 (1.07–1.19)	0.009
	female	229,252	9,687	1.11 (1.05–1.16)	
Prostate cancer					
Ever had PSA[c] test	yes	54,201	3,986	1.00 (0.92–1.09)	0.007
	no	134,607	5,125	1.14 (1.05–1.23)	
Brain cancer					
Overall health rating	Excellent	72,629	113	0.80 (0.49–1.31)	0.021
	Fair	83,321	126	1.22 (0.77–1.92)	
	Good	245,649	398	0.94 (0.72–1.23)	
	Poor	16,461	28	Not estimated[d]	

[a]All sensitivity analyses were performed using the full model adjusted for sociodemographic variables (including gender, ethnicity, education and Townsend Deprivation Index), lifestyle factors (including smoking, alcohol consumption, vegetable consumption, processed meat intake, fresh fruit intake, vitamin supplements, mineral supplements, body mass index, and physical activities), and medical conditions and services (including diagnosis of osteoarthritis/rheumatoid arthritis/joint pain/multiple sclerosis, history of screening for bowel cancer/breast cancer/prostate-specific antigen test, use of aspirin/NSAIDs/hormone-replacement therapy, family history of cancer, and overall health rating).

[b]The potential effect modifications were assessed by modeling the cross-product term of the stratifying covariate with glucosamine use in the full model. $P < 0.05$ for interaction was considered statistically significant.

[c]Abbreviation: PSA, prostate-specific antigen.

[d]Not estimated due to no events among the glucosamine users.

were only 1,466 participants with diagnosis of more than two cancers in this study, which should not substantially affect our main findings. Third, although we have controlled for multiple covariates in the models, unmeasured residual confounding may still exist. Fourth, a low response rate in the UK Biobank may have compromised the representativeness of our study population since it has been noted that UK Biobank participants were more likely to be older, to be female, to live in less socioeconomically deprived areas and to have a healthier lifestyle than the UK population (39). However, a previous study showed that risk factor associations in the UK Biobank seemed comparable with those from other prospective studies with higher response rates. In addition, the association between glucosamine use and risk of lung cancer observed in the UK Biobank were consistent with that based on the VITAL cohort (12, 13). These consistent findings suggested the associations observed in our study would not be necessarily influenced by insufficient representativeness of the UK population (40). Fifth, we did not adjust statistical threshold for multiple hypothesis testing, and thus some of our findings at a statistical threshold of $P < 0.05$ may exaggerate the association, which should be interpreted with caution. Given the large sample size of the UK Biobank, some statistically significant associations or interactions may not be clinically relevant.

In conclusion, regular glucosamine use was associated with increased risk of overall cancer. For site-specific cancers, regular glucosamine use was associated with lower risk of lung cancer but higher risk of skin cancer and prostate cancer. These important findings suggest that glucosamine may not be consistently beneficial for the prevention of different site-specific cancers.

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Authors' Contributions

F.-X. Li: Conceptualization, data curation, software, formal analysis, funding acquisition, investigation, visualization, methodology, writing–original draft, writing–review and editing. **H.-Y. Zhao:** Investigation, methodology, writing–review and editing. **T.-F. Lin:** Methodology, writing–review and editing. **Y.-W. Jiang:** Methodology, writing–review and editing. **D. Liu:** Methodology, writing–review and editing. **C. Wei:** Data curation, software, validation. **Z.-Y. Zhao:** Data curation, software, validation. **Z.-Y. Yang:** Methodology, writing–review and editing. **F. Sha:** Supervision, methodology, project administration, writing–review and editing. **Z.-R. Yang:** Conceptualization, supervision, funding acquisition, validation, investigation, methodology, writing–original draft, project administration, writing–review and editing. **J.-L. Tang:** Resources, supervision, funding acquisition, methodology, project administration, writing–review and editing.

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Note

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

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