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Supplement Use and Gastric Cancer Risk in the Southern Community Cohort Study

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Abstract

Purpose—Gastric cancer remains a racial health disparity in the US, but few studies have examined supplements as a potential protective factor. We examined associations between regular supplement use and gastric cancer risk among the predominantly Black participants in the Southern Community Cohort Study (SCCS).

Methods—Of the 84,508 individuals recruited in the SCCS from 2002-2009, 81,884 responded to the baseline question: any vitamin or supplement taken at least once per month in the past year. Secondary analyses assessed specific supplement use. Associations with incident gastric cancer were examined using adjusted Cox proportional hazards models, stratified by histologic subtype and secondarily by Healthy Eating Index (HEI).

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Authorship Contributions

Jessica Goodwin, Martha Shrubsole, and Meira Epplein contributed to the study conception and design. Material preparation and data collection were overseen by Martha Shrubsole and Meira Epplein. Data analyses were performed by Jessica Goodwin and Qichen Wang. Pao-Hwa Lin contributed important content knowledge, and advised on the analyses. The first draft of the manuscript was written by Jessica Goodwin and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval

This study received approval from the Duke University Health System Institutional Review Board for Clinical Investigations (Pro00110089).

Consent to Participate

Informed consent was obtained from all participants.

Results—Approximately half of the participants (47%, n=38,318) reported any regular supplement use. Among the 203 incident gastric cancers over the follow-up period (median, 7 years), 142 were non-cardia (NCGC), 31 cardia (CGC), and 30 unknown. Regular supplement use was associated with a 30% decreased risk of NCGC (hazards ratio (HR), 0.70; 95% confidence interval (CI), 0.49–0.99). Among participants below the HEI median, any regular supplement and multivitamin use were associated with a 52% and 70% decrease in risk of NCGC (HR, 0.48; 95% CI, 0.25-0.92 and HR, 0.30; 95% CI, 0.13-0.71), respectively. No associations were found for CGC.

Conclusion—Regular supplement use, including multivitamins, was associated with a decreased risk of NCGC in the SCCS, particularly among participants with a lower quality diet. Inverse associations of supplement use and NCGC incidence provide support for clinical trials among high-risk populations in the US.

Keywords

vitamin; supplement; gastric cancer; risk; disparity; low-income

Introduction

In 2020, GLOBOCAN estimated one million new gastric cancer cases and 769,000 deaths from gastric cancer (1 in 13 deaths from cancer), thus ranking gastric cancer as fifth for incidence and fourth for mortality among all cancer cases globally.(1) While the incidence of gastric cancer in the US is decreasing, mortality is still high as gastric cancer is usually diagnosed at a late stage; only 32.4% of patients survive 5 years.(2) Furthermore, racial and gender disparities for gastric cancer remain prominent.(3) In the American Cancer Society's 2022 report of cancer incidence in Black/African American people, Black men were 1.8 times more likely to develop gastric cancer compared to White men, and Black women were 2.1 times more likely to develop gastric cancer than White women.(3) Of the five racial/ethnic categories as used by the Surveillance, Epidemiology, and End Results (SEER) Program, Black men are at the second highest risk of gastric cancer incidence (13.4 per 100,000) and the second highest rate of mortality (7.3 per 100,000) compared to any other race or gender; non-Hispanic Native American/Alaskan Native were the highest for incidence and mortality.(2)

The most well-established risk factors for gastric cancer are older age, cigarette smoking, and infection with *Helicobacter pylori (H. pylori)*, a gram-negative, spiral bacteria that chronically infects approximately 30% of the US population.(2, 4) Inverse associations found in observational studies of a diet high in fruits and vegetables with gastric cancer incidence led to a clinical trial of supplementation to reduce gastric cancer risk in a high-risk area of China.(5) In this randomized study, the Shandong Intervention Trial, approximately 3,400 participants, ages 35-70, were recruited in 1995 to assess the effects of *H. pylori* treatment, supplementation (vitamin C, vitamin E, and selenium), and garlic extract on risk and mortality of gastric cancer in a high gastric cancer risk, nutrient-deficient Chinese population.(6, 7) In the most recent, 22-year follow-up of the trial, Li et al found that supplements were associated with decreased incidence of gastric cancer (OR, 0.64; 95% CI, 0.46-0.91) while garlic supplements were not (OR, 0.81; 95% CI, 0.57-1.13), although both

were associated with decreased gastric cancer mortality (HR, 0.48; 95% CI, 0.31-0.75 and HR, 0.66; 95% CI, 0.43-1.00, respectively).(6) The inverse associations with vitamin and garlic supplementation and gastric cancer mortality only became evident approximately 8 years after treatment, suggesting the potential protection is strongest for individuals who are earlier along the gastric cancer cascade prior to diagnoses of intestinal metaplasia or gastric cancer.

In the US, there have been few studies to assess the association of supplement use and gastric cancer risk and none in systematically underserved and high-risk groups. However, the association of circulating micronutrients and *H. pylori* status, including sero-positivity to the virulent CagA-positive *H. pylori*, has been explored among participants in the Southern Community Cohort Study (SCCS), a prospective cohort study of predominantly Black/African American and low-income individuals in the southeast US. Epplein et al. found an association between *H. pylori* sero-positivity, particularly CagA sero-positivity, and lower levels of circulating nutrients (β-carotene, folate, total carotenoids, and retinol), although with no corresponding difference in dietary intake.(8) These findings support the hypothesis that long-term infection of *H. pylori* impairs nutrient absorption due to its ability to increase pH in the stomach.(8–10) Recently, a comprehensive meta-analysis and systematic review of 48 articles published from 1991 to 2021 analyzed the association between supplements and *H. pylori*.(11) They found that *H. pylori* infection was associated with lower serum levels of several nutrients including vitamin C.(11) Additionally, supplementation of an antioxidant (vitamin C) improved eradication rates of *H. pylori*.(11)

In the present study, we sought to examine the association between regular supplement use and gastric cancer risk among the under-studied and predominantly high-risk population of the SCCS. With recognition of the differing etiologies by histologic sub-site, we sought to further explore the association of supplements with risk of non-cardia gastric cancer (NCGC) and cardia gastric cancer (CGC), separately. Finally, due to the frequency of specific supplement, we also estimated the individual associations of use of multivitamins, vitamin C, vitamin E, calcium supplements, and garlic supplements with incident gastric cancer use based on *a priori* hypotheses.

Methods

Southern Community Cohort Study

The SCCS recruited approximately 85,000 participants, ages 40-79, in the southeast region of the US during 2002-2009 to address health disparities in cancer and other major diseases.(12) This population is predominately low-income, born in the US, and two-thirds of participants self-report as Black/African American. Informed consent was obtained from all participants. The SCCS was approved by Institutional Review Boards at Vanderbilt University Medical Center and Meharry Medical College. Baseline questionnaires were completed through in-person, computer-assisted interviews at community health clinics (86%) and randomly sampled by mail for the general population (14%). Neighborhood deprivation index was calculated according to Signorello et al. after using principal components analysis and was based on 11 census-tract level variables: percentage of persons that did not graduate high school (age ≥25 years), percentage of males and females who

are unemployed, percentage of males in professional occupations, percentage of housing units with ≥1 occupant per room, percentage of occupied housing units with renter/owner costs >50% of income, percentage of persons with income below the 1999 poverty status, percentage of female headed households with dependent children, percentage of households with income <$30,000 per year, percentage of households with public assistance income, percentage of households with no car, and median household value.(13, 14) As performed in previous SCCS studies, participants were divided into neighborhood deprivation quartiles based on the distribution of neighborhood deprivation index values of all census tracts in the 12 SCCS states, with the first (lowest) quartile representing the least deprived areas.[14]

Data linkages to cancer registries across the 12-state catchment area were used to assess gastric cancer incidence following enrollment. Incident gastric cancer was categorized by histologic site: NCGC and CGC. Analyses were conducted among all cases and by gastric cancer site.

Assessment of Supplement Use

Our primary exposure of interest was any regular supplement use, which was defined by the answer “yes” to the SCCS survey question, “During the past year, have you taken any vitamin, mineral, herbal, or other nutritional supplements at least once a month?”. Only 3% of the 84,508 SCCS participants declined to answer this question, leaving 81,884 individuals for the present study. The secondary exposures included use of the following: multivitamins (including, but not limited to, One-a-day, Centrum, Thera type, Stresstab, or B-complex type); vitamin C; vitamin E; calcium supplements; and garlic pills. Frequency of taking specific supplements were assessed over the past year, which we categorized as never/rarely (includes the responses: never, rarely, and not applicable) and sometimes/always (at least once per month). Excluding missing values, which ranged from 2-4%, 38% of participants took multivitamins (n= 29,949); 15% took vitamin C (n= 12,044), 14% took vitamin E (n= 11,252), 15% took calcium supplements (n= 11,665), and 5% took garlic pills (n= 4,279).

Statistical Analysis

Comparison of baseline characteristics by gastric cancer status and regular supplement use was evaluated using the Chi-square test for categorical variables, unless the cells were too small, in which case the Fisher Exact test was used. The ANOVA F test was used to compare differences among the continuous variables.

To calculate hazards ratios (HR) and 95% confidence intervals (CIs) for the association of supplement use and the risk of developing gastric cancer, we used Cox proportional hazards regression models with the time scale as the difference in enrollment age and age at gastric cancer, death, or last follow-up. The proportional hazard assumption was met by examining the correlations between the rank of difference in enrollment age and Schoenfeld residuals, and p-values were rounded to two decimal places and compared with alpha level at 0.05. Our primary exposure of interest was any regular supplement use, defined as having taken any vitamin, mineral, herbal, or other nutritional supplements at least once a month, compared to supplement use of less than once a month. We also explored the association of use of specific supplements, including multivitamin, vitamin C,

vitamin E, calcium, and garlic pills. For each specific supplement, we compared sometimes or always use with rarely to never use (reference value). The following covariates were *a priori* chosen to be considered as potential confounders in the adjusted models: age, race, sex, smoking status (ever/never), alcohol use during the time period when alcohol was most frequently consumed (never/rarely, 1-3x per month, 1-4x per week, and daily/nearly daily), diabetes (yes/no), ulcer (yes/no), reflux (yes/no), health insurance coverage (yes/no), and first-degree family history of gastric cancer (yes/no and unknown). Separating ever smoking into current and former smoking was examined, but there was no difference in the association with gastric cancer risk between the two variables. Additional *a priori* covariates were assessed, including BMI (<30/≥30), dietary intake data from FFQ (vegetables per day and fruits per day), household income (<$15,000/≥ $15,000), education (high school degree or less/more than high school degree), and enrollment source (community health clinic/general population), but were not significant on their own nor did they impact the HR for the main exposure by more than 10%, and thus were not included in the final models. Additionally, Healthy Eating Index (HEI) was calculated for 77,376 participants (HEI was not calculated for 5.5% of the population, n=4,508) and was used for stratified analyses concerning the association between supplement use and NCGC The HEI-2010 recommended increasing consumption of nine components: total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and the ratio of unsaturated to saturated fatty acids; and decreasing consumption of three components: refined grains, sodium, and empty calories from solid fats, alcohol, and added sugars.(15) The 12 components of HEI-2010 sum to a total maximum score of 100. Additionally, dietary intake of vitamin C, calcium, and garlic as assessed from the FFQ were considered in the analyses, but again were not found to be confounders in the association between supplements and gastric cancer risk.

In the analysis of disease risk, individuals contributed follow-up time from enrollment until incident cancer, death, or last follow-up. As noted above, separate models were created for all incident gastric cancers, and for NCGC and CGC separately. Models were adjusted for variables determined to be confounders for each model, as described above. Association analyses were also stratified by sex, race, and median HEI value. The data analysis for this paper was generated using SAS software, version 9.4. Copyright (© 2020 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided, and associations resulting in a $p < 0.05$ were considered statistically significant.

Results

Demographics and baseline characteristics by case status

Of the 81,884 SCCS participants included in these analyses, 203 developed gastric cancer over the follow-up period, on average (median) 7 years after baseline (inter-quartile range, 4-10 years). By histologic subtype, there were 142 NCGC, 31 CGC, and 30 designated as unknown. Compared to the underlying cohort, there were many differences among the gastric cancer cases by histologic subtype (Table 1). Both NCGC and CGC cases were more likely to be older, to be male, and to have ever smoked compared to the general

SCCS cohort. Participants who developed NCGC were also more likely to identify as Black/African American, to have a lower education (high school diploma or less), to have health insurance coverage, and to have been diagnosed with diabetes or a stomach/small intestine ulcer, than the general SCCS cohort. Participants with CGC were more likely to identify as white, and when comparing gastric cancer cases by subtype, there was a significant difference in prevalence by race, with the majority of NCGC cases identifying as Black/African American (80%) versus the majority of CGC cases identifying as white (65%). There was little self-report of family history of gastric cancer, and no significant difference in alcohol consumption or BMI by across all cohorts.

Supplement use in the SCCS

Just less than half (47%) of the SCCS participants who answered the survey question on supplement use reported any regular use (Table 2). Compared to non-regular supplement users, regular supplement users were more likely to be older (average of 2 years), to be female, to identify as white, to have a lower BMI, to have some college education or have completed a collegiate degree, to have a higher household income, and to have insurance coverage. Regular supplement users were less likely to live in an area with the greatest deprivation index and to have diabetes than non-regular users but were more likely to have been diagnosed with an ulcer or reflux. Regular supplement users were also more likely to be never or former smokers and less likely to be daily or nearly daily alcohol users compared to non-regular supplement users.

Regular supplement use and gastric cancer incidence

In the final model for all incident gastric cancer cases, adjusting for age, sex, smoking status, and diabetes, regular supplement use was associated with a non-significant 21% reduction in the risk of developing gastric cancer (HR, 0.79; 95% CI, 0.60–1.05) (Table 3). When stratified by histological subtype, the final model for NCGC included race and history of ulcer, in addition to the variables included in the model for all gastric cancers and found that regular supplement use was associated with a statistically significant 30% decrease in the risk of NCGC (HR, 0.70; 95% CI, 0.49-0.99). The final adjusted model for CGC on the other hand, which included age, race, and sex, did not find any association with regular supplement use (HR, 0.93; 95% CI, 0.45–1.92).

No significant associations were found for sometimes or always use of the specific supplements (multivitamin, vitamin C, vitamin E, calcium, and garlic pills) and risk of NCGC or CGC (Table 4). However, there was a suggestion that use of garlic pills was associated with a decreased risk of developing NCGC (HR, 0.33; 95% CI, 0.11–1.05), although only a small percentage of this population were users of garlic pills. No associations were suggested between supplement use and CGC.

When further stratified by HEI, regular supplement use was associated with a statistically significant 52% reduction in risk of NCGC for individuals with below-median HEI scores (HR, 0.48; 95% CI, 0.25-0.92) (Table 5). Additionally, for these individuals with below-median HEI scores, sometimes or always multivitamin use was associated with a statistically significant 70% reduction in risk of NCGC (HR, 0.30; 95% CI, 0.13-0.71). There were no

significant associations with supplement use for individuals with HEI scores above or equal to the median, although there was a suggestive reduction in NCGC risk with regular use of garlic pills (HR, 0.29; 95% CI, 0.07-1.17). HEI analyses were not conducted for CGC, due to the small numbers. It is relevant to note that the median HEI-2010 for this cohort was 57.53 which was higher (more favorable) than the national mean averages for adults ages 18-64 reported in 2005-2006 and 2007-2008 (53.67 and 54.30, respectively) and equivalent to the national mean averages reported in 2009-2010.(16)

Additionally, no differences were found in the association of supplement use and risk of gastric cancer in analyses stratified by sex and race (see Supplemental Tables 1 and 2). A sensitivity analysis excluding cases diagnosed within one year of baseline also did not reveal a difference in the association of supplement use and gastric cancer risk (data not shown).

Discussion

In the present study, we found that regular supplement use was inversely associated with incident NCGC in an under-served and high-risk population in the southeast US, with no variation in the association by race or sex, and this association was particularly strong among individuals with a lower quality diet. We did not find an association of regular supplement use with incident CGC, however this constituted a much smaller group of cases in this population.

This is the first study to examine the association of supplement use and risk of gastric cancer in the SCCS, a cohort with a primarily USA-born and two-thirds Black/African American population. While there was a statistically significant racial difference in the incidence of NCGC and CGC, the association between supplementation and NCGC did not differ by race (and we were not powered to examine the difference by race for CGC). In addition, men were more likely to develop gastric cancer, but stratification by sex did not reveal differences in the association with supplement use between men and women.

Previous studies of the association of supplement use and gastric cancer risk in the US have been explored primarily in the prospective cohort in the NIH-AARP Diet and Health Study.(17, 18) In a NIH-AARP study of 245 NCGC cases and 209 CGC cases, Dawsey et al. reported that frequent multivitamin use was associated with a decreased risk of NCGC, although after adjustment it was no longer significant (more than once a day compared to never HR, 0.65; 95% CI, 0.39-1.08; p-value, 0.15).(18) Similarly, in a predominately white population in the northeast US, including 352 NCGC cases and 255 CGC cases, Mayne et al. likewise found no significant associations between specific multivitamins (One-A-Day, Stress types, and Theragran) and NCGC or CGC.(19) In the present study, we found a similar, non-significant association between multivitamins and NCGC (HR, 0.73; 95% CI, 0.50-1.06; p-value, 0.10) prior to stratifying by HEI. After stratifying by HEI, we found that individuals with HEI scores below the median who were multivitamin users had a significant 70% reduction in gastric cancer incidence, whereas there was no significant protection afforded by multivitamin use among individuals with above-median HEI scores. In all of these cohorts, the heterogeneity of multivitamins remains a limitation.(18)

Examinations of vitamin C and vitamin E supplement and gastric cancer risk have produced varied results. For vitamin C supplement users, Dawsey et al. found a significant 21% reduction in risk of NCGC (HR, 0.79; 95% CI, 0.65-0.96) in the NIH-AARP, whereas we did not detect that association in the present study (HR, 0.91; 95% CI, 0.55-1.51).(18) Of note, compared to the SCCS, the NIH-AARP cohort is predominately white (whereas the SCCS is only 30% self-identified as white) and of older age (median age at baseline of 62 compared to 51 in the SCCS).(18) Other studies with different populations have also found that vitamin C supplements have an inverse association with gastric cancer risk.(18–20) Mayne et al. assessed supplement use defined as taking specific supplements at least once per week for 6 or more months (which is a higher frequency than as defined in the present study).(19) Mayne et al. found that vitamin C supplements were associated with a decreased risk for NCGC (OR, 0.60; 95% CI, 0.41–0.88) but not with CGC.(19) Mayne et al. did not see an association between vitamin E supplements and gastric cancer.(19) We did not find associations for vitamin C or vitamin E supplements in the SCCS. Like the present study, Mayne et al. discussed that they were not able to attain the dosage for each supplement taken.(19)

Studies of calcium supplements and gastric cancer risk have produced conflicting findings. Comprising 1,518 gastric adenocarcinoma cases among 536,403 participants in the NIH-AARP cohort, Shah et al. found that above median total calcium intake (>881.3 mg), calculated from combined dietary intake and supplement use, was associated with an 18% decreased risk for adenocarcinoma and a 23% decrease for NCGC specifically.(17) They suggest that patients who identify or are characterized by the following may benefit from increased calcium intake: males, individuals of Hispanic ethnicity and non-white race, BMI ≥ 30, current/former smokers, and moderate/heavy drinkers.(17) In Dawsey et al.'s separate NIH-AARP study, comprising 245 NCGC cases and 209 CGC cases, calcium supplements alone were associated with 27% increase in CGC risk (HR, 1.27; 95% CI, 1.03-1.56) but had no association with NCGC (HR, 0.94; 95% CI, 0.77-1.16) when adjusting for age, sex, education, smoking status, alcohol use, fruit and vegetable intake, physical activity, BMI, and total energy intake.(18) Dawsey et al. noted that calcium supplements may be included in reflux treatments; yet, in the present study, we found no associations between calcium supplements and NCGC or CGC, even after adjusting for self-reported reflux.(18)

In the present study, we found a suggestive inverse association between garlic supplements and NCGC in participants with a HEI of 57.53 or greater. An international meta-analysis found a significant association between garlic intake through diet and NCGC (OR, 0.83; 95% CI, 0.75-0.93) but only in studies with Asian populations.(21) This meta-analysis noted that there was insufficient data collection on garlic intake in US studies.(21) As noted above, In the Shandong Intervention Trial in China, researchers did not find a significant association between garlic extract supplements and gastric cancer incidence, but did see a protective effect of garlic extract with gastric cancer mortality when examining outcomes 22 years after the intervention.(6) We do not know of studies that have assessed garlic supplement use and NCGC or CGC incidence in a US population.

Since *Helicobacter pylori* infection is a prominent risk factor for NCGC, it is a limitation that the present study, similar to the studies discussed above, was unable to control for

this variable. To note, *H. pylori* is highly prevalent in the SCCS, with estimations of 79% sero-prevalence overall(22), and moreover previous studies have found that *H. pylori* status did not affect the association of supplementation and gastric cancer risk.(6, 20)

Other limitations include lack of detailed supplement data, such as dosage, duration of supplement use, and type of multivitamin most commonly consumed in this cohort (acknowledging as multivitamins a heterogeneous category). We were also unable to categorize supplement use into more finely detailed categories, such as five days a week or more, due to the small numbers of gastric cancer cases in this group. Supplement use may also be linked to other health-promoting behaviors that were not outlined in this study, potentially resulting in unmeasured confounding. Potential changes in health conditions over time could not be assessed given the use of baseline measurement of supplement use. We were also not statistically powered to examine other supplements of interest (A, B6, D, folate, selenium, etc.) because few participants reported use of at least once per month for other supplements, and our small numbers overall for this rare disease meant that our statistical power was limited for stratified analyses. Finally, without knowledge of circulating nutrient levels, we do not know which participants have deficiencies or if the supplements are being adequately absorbed. It is worth considering the potential effect that undiagnosed gastric cancer may have on dietary habits. As a strength, we were able to control for dietary habits by stratifying by HEI in the present analysis.

Conclusion

Regular supplement use was associated with a decreased risk of NCGC in the SCCS. Among participants with below-median HEI scores, both any regular supplement use and multivitamin use was associated with a decreased risk of NCGC. There was a non-statistically significant suggestion that garlic pills also decreased the risk for NCGC. Our data did not show an association between vitamin C, vitamin E, or calcium supplements and risk of the gastric cancer in either histologic group. There are few studies that examine the use of supplements to prevent gastric cancer in a diverse, low-income population within the US. Additional studies that assess circulating nutrient levels should be considered to further determine the potential effect of supplementation for participants with vitamin deficiencies. It may also be necessary to evaluate the absorbability of supplements for participants, particularly those with *H. pylori* infection. Nonetheless, the associations found in the present study support the consideration of clinical trials to further examine the possibility of supplementation to reduce gastric cancer risk in high-risk populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

This dataset and the use of SCCS data more broadly is granted through applications to the SCCS DBU and investigators wishing to use data are welcome to apply.

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Table 1.

Baseline Characteristics of SCCS Participants by Gastric Cancer Status

	Control Cohort (n = 81,681)				Gastric Cancer Cases (n = 203) *							
					Non-Cardia (n = 142)				Cardia (n = 31)			
	N	%	Mean	STD	N	%	Mean	STD	N	%	Mean	STD
Age at enrollment, years [a]			52	8.8			58	9.6			59	8.0
Sex [b]												
Female	48,515	59.4			71	50.0			8	25.8		
Male	33,166	40.6			71	50.0			23	74.2		
Race [b]												
White	24,649	30.2			25	17.6			20	64.5		
Black/African American	53,372	65.3			113	79.6			10	32.3		
Other (His, As, NA, Mix)	3,233	4.0			1	0.7			1	3.2		
Unknown	427	0.5			3	2.1			0	0.0		
Body mass index, [kg/m^2]			30.3	7.5			29.4	7.4			29.5	7.7
Education [c]												
Less than high school/GED	23,221	28.4			53	37.3			8	25.8		
High School	26,700	32.7			50	35.2			11	35.5		
Some/Junior college	20,656	25.3			19	13.4			5	16.1		
College degree	6,596	8.1			10	7.0			4	12.9		
More than college	4,086	5.0			6	4.2			3	9.7		
Unknown	422	0.5			4	2.8			0	0		
Household income												
<$15,000	44,290	54.2			75	52.8			16	51.6		
$15,000 – <$25,000	16,956	20.8			36	25.4			6	19.4		
$25,000 – <$50,000	11,400	14.0			18	12.7			3	9.7		
$50,000 – <$100,000	5,891	7.2			6	4.2			4	12.9		
≥$100,000	1,959	2.4			3	2.1			2	6.5		
Unknown	1,185	1.5			4	2.8			0	0.0		
Insurance [c]												
No	31,852	39.0			43	30.3			12	38.7		
Yes	49,712	60.9			99	69.7			19	61.3		
Unknown	117	0.1			0	0.0			0	0.0		
Geographic Deprivation Index Group (Quartile)												
Q1	8,695	10.7			7	4.9			7	22.6		
Q2	12,979	15.9			23	16.2			4	12.9		
Q3	17,036	20.9			25	17.6			5	16.1		

	Control Cohort (n = 81,681)				Gastric Cancer Cases (n = 203) *							
					Non-Cardia (n = 142)				Cardia (n = 31)			
	N	%	Mean	STD	N	%	Mean	STD	N	%	Mean	STD
Q4	41,806	51.2			83	58.5			14	45.2		
Unknown	1,165	1.4			4	2.8			1	3.2		
Family history of gastric cancer												
No/unknown	79,083	96.8			136	95.8			31	100.0		
Yes	2,598	3.2			6	4.2			0	0.0		
Diabetes[c]												
No	64,238	78.6			97	68.3			24	77.4		
Yes	17,406	21.3			45	31.7			7	22.6		
Unknown	37	0.1			0	0.0			0	0.0		
Ulcer[c]												
No	71,329	87.3			114	80.3			29	93.6		
Yes	10,266	12.6			27	19.0			2	6.5		
Unknown	86	0.1			1	0.7				0.0		
Reflux												
No	58,875	72.1			104	73.2			22	71.0		
Yes	22,760	27.9			38	26.8			9	29.0		
Unknown	46	0.1			0	0.0			0	0.0		
Smoking Status[b]												
Never	29,266	35.8			37	26.1			5	16.1		
Former	18,684	22.9			48	33.8			13	41.9		
Current, <20 cigs/day	21,208	26.0			37	26.1			4	12.9		
Current, ≥20 cigs/day	11,802	14.5			17	12.0			9	29.0		
Unknown	721	0.9			3	2.1			0	0.0		
Alcohol												
Never/Rarely	24,138	29.6			41	28.9			6	19.4		
1-3 times per month	8,199	10.0			10	7.0			2	6.5		
1-4 times per week	25,564	31.3			47	33.1			9	29.0		
Daily/Nearly Daily	23,111	28.3			43	30.3			14	45.2		
Unknown	669	0.8			1	0.7			0	0.0		

*The 30 gastric cancers with unknown site were excluded from this table, and further analyses.

[a]P < 0.05 for both NCGC and CGC compared to the control cohort, ANOVA F test.

[b]P < 0.05 for both NCGC and CGC compared to the control cohort, Chi-Square test, two-sided.

[c]P < 0.05 for NCGC compared to the control cohort, Chi-Square test, two-sided.

Table 2.

Baseline Characteristics of SCCS Participants by Regular Supplement Use

	Non-Regular Supplement Users (n = 43,566)				Regular Supplement Users (n = 38,318)			
	N	**%**	**Mean**	**STD**	**N**	**%**	**Mean**	**STD**
Age at enrollment, years[a]			51	8.6			53	8.9
Sex[b]								
Female	24,209	55.6			24,398	63.7		
Male	19,357	44.4			13,920	36.3		
Race[b]								
White	11,276	25.9			13,428	35.0		
Black/African American	30,743	70.6			22,770	59.4		
Other (His, As, NA, Mix)	1,420	3.3			1,817	4.7		
Unknown	127	0.3			303	0.8		
Body mass index, [kg/m2][a]			30.5	7.7			30.1	7.3
Education[b]								
Less than high school/GED	15,491	35.6			7,799	20.4		
High School	15,320	35.2			11,449	29.9		
Some/Junior college	9,087	20.9			11,603	30.3		
College degree	2,384	5.5			4,229	11.0		
More than college	1,149	2.6			2,947	7.7		
Unknown	135	0.3			291	0.8		
Household income[b]								
<$15,000	27,303	62.7			17,096	44.6		
$15,000 – <$25,000	8,876	20.4			8,126	21.2		
$25,000 – <$50,000	4,554	10.5			6,871	17.9		
$50,000 – <$100,000	1,809	4.2			4,094	10.7		
≥$100,000	495	1.1			1,470	3.8		
Unknown	529	1.2			661	1.7		
Insurance[b]								
No	18,800	43.2			13,116	34.2		
Yes	24,701	56.7			25,150	65.6		
Unknown	65	0.2			52	0.1		
Geographic Deprivation Index Group (Quartile)[b]								
Q1	3,270	7.5			5,444	14.2		
Q2	6,156	14.1			6,855	17.9		
Q3	8,846	20.3			8,223	21.5		
Q4	24,852	57.0			17,067	44.5		
Unknown	442	1.0			729	1.9		

	Non-Regular Supplement Users (n = 43,566)				Regular Supplement Users (n = 38,318)			
	N	%	Mean	STD	N	%	Mean	STD
Family history of gastric cancer								
No/unknown	42,199	96.9			37,080	96.8		
Yes	1,367	3.1			1,238	3.2		
Diabetes[b]								
No	33,825	77.6			30,557	79.8		
Yes	9,724	22.3			7,741	20.2		
Unknown	17	0.04			20	0.05		
Ulcer[b]								
No	38,363	88.1			33,133	86.5		
Yes	5,153	11.8			5,148	13.4		
Unknown	50	0.1			37	0.1		
Reflux[b]								
No	32,732	75.1			26,289	68.6		
Yes	10,812	24.8			12,005	31.3		
Unknown	22	0.1			24	0.1		
Smoking Status[b]								
Never	14,169	32.5			15,143	39.5		
Former	8,592	19.7			10,167	26.5		
Current, <20 cigs/day	12,877	29.6			8,378	21.9		
Current, ≥20 cigs/day	7,661	17.6			4,172	10.9		
Unknown	267	0.6			458	1.2		
Alcohol[b]								
Never/Rarely	12,668	29.1			11,522	30.1		
1-3 times per month	4,145	9.5			4,069	10.6		
1-4 times per week	13,346	30.6			12,283	32.1		
Daily/Nearly Daily	13,117	30.1			10,064	26.3		
Unknown	290	0.7			380	1.0		

[a] $P < 0.05$ comparing non-regular supplement users to regular supplement users, ANOVA F test.

[b] $P < 0.05$ comparing non-regular supplement users to regular supplement users, Chi-Square test, two-sided.

Table 3.

Final Adjusted Models for the Association of Regular Supplement Use and Incident Gastric Cancer

	HR (95% CI)		
	All Gastric Cancer (n = 203 cases)	**Non-Cardia Gastric Cancer (n = 142 cases)**	**Cardia Gastric Cancer (n = 31 cases)**
Regular Supplement User	0.79 (0.60-1.05)	0.70 (0.49-0.99)	0.93 (0.45-1.92)
Older age	1.08 (1.06-1.09)	1.08 (1.06-1.10)	1.08 (1.04-1.12)
Black Race	-	2.57 (1.66-4.00)	0.28 (0.13-0.61)
Female Sex	0.58 (0.43-0.77)	0.66 (0.47-0.93)	0.21 (0.09-0.46)
Ever Smoker	2.04 (1.41-2.78)	1.70 (1.15-2.52)	-
Diagnosed with stomach or small intestine ulcer	-	1.53 (0.99-2.34)	-
Diagnosed with Diabetes	1.38 (1.01-1.89)	1.45 (1.00-2.10)	-

Table 4.

Associations between Use of Specific Supplements and Incident Gastric Cancer by Histologic Site among Participants in the SCCS

	Non-Cardia Gastric Cancer [a]					Cardia Gastric Cancer [b]				
	Events	Person-years*	HR [a]	95% CI	P-value	Events	Person-years*	HR [b]	95% CI	P-value
Any Supplement										
Rarely/never	84	503,945	REF			15	507,543	REF		
Sometimes/always	52	446,374	0.70	0.49-0.99	0.04	16	451,749	0.93	0.45-1.92	0.85
Multivitamin										
Rarely/never	94	577,004	REF			16	581,089	REF		
Sometimes/always	41	351,074	0.73	0.50-1.06	0.10	14	354,325	1.16	0.56-2.39	0.70
Vitamin C										
Rarely/never	113	779,663	REF			25	785,206	REF		
Sometimes/always	18	142,336	0.91	0.55-1.51	0.73	5	144,418	0.84	0.32-2.20	0.72
Vitamin E										
Rarely/never	116	788,044	REF			25	793,658	REF		
Sometimes/always	15	134,359	0.74	0.43-1.28	0.28	4	136,262	0.70	0.24-2.02	0.50
Calcium										
Rarely/never	119	786,549	REF			26	792,091	REF		
Sometimes/always	12	138,117	0.61	0.33-1.12	0.11	3	140,069	0.56	0.16-1.91	0.36
Garlic pills										
Rarely/never	127	864,534	REF			28	870,995	REF		
Sometimes/always	3	51,018	0.33	0.11-1.05	0.06	1	51,679	0.49	0.07-3.61	0.48

[a] HR adjusted for enrollment age, race (black/white), sex, smoking status (ever/never), diagnosis of stomach or small intestine ulcer, diagnosis of diabetes

[b] HR adjusted for enrollment age, race (black/white), and sex

* Person-years is calculated based records with non-missing covariates that are used for adjustment respectively

Table 5.

Associations between Use of Specific Supplements and Incident Non-Cardia Gastric Cancer among Participants in the SCCS, stratified by HEI level

	Non-Cardia Gastric Cancer									
	Healthy Eating Index < Median [a]					Healthy Eating Index ≥ Median [a]				
	Events	Person-years*	HR [b]	95% CI	P-value	Events	Person-years*	HR [b]	95% CI	P-value
Any Supplement										
Rarely/never	44	281,673	REF			40	193,078	REF		
Sometimes/always	12	166,111	0.48	0.25-0.92	0.03	36	259,757	0.70	0.44-1.10	0.12
Multivitamin										
Rarely/never	50	311,882	REF			44	232,891			
Sometimes/always	6	129,337	0.30	0.13-0.71	0.01	31	206,976	0.84	0.53-1.34	0.48
Vitamin C										
Rarely/never	53	395,763	REF			58	343,335			
Sometimes/always	3	43,714	0.58	0.18-1.86	0.36	13	91,650	0.92	0.50-1.69	0.78
Vitamin E										
Rarely/never	54	399,380	REF			59	347,591			
Sometimes/always	2	40,075	0.38	0.09-1.56	0.18	12	87,899	0.83	0.44-1.55	0.55
Calcium Supplement										
Rarely/never	54	400,958	REF			62	343,793			
Sometimes/always	2	38,853	0.49	0.12-2.03	0.32	9	93,525	0.56	0.27-1.15	0.11
Garlic Pills										
Rarely/never	55	424,926	REF			68	395,134			
Sometimes/always	1	12,716	0.53	0.07-3.81	0.53	2	36,060	0.29	0.07-1.17	0.08

[a] HEI Median is 57.53, and it was calculated based on 81,884 subjects with non-missing HEI value, i.e., the median of (81884-4508 = 77,376) participants HEI value

[b] HR adjusted for enrollment age, race (black/white), sex, smoking status (ever/never), diagnosis of stomach or small intestine ulcer, diagnosis of diabetes

* Person-years is calculated based records with non-missing covariates that are used for adjustment, respectively