Published in final edited form as:
Eur J Cancer. 2009 July ; 45(10): 1824–1830. doi:10.1016/j.ejca.2009.01.027.

Genetic variation in sodium-dependent ascorbic acid transporters and risk of gastric cancer in Poland

Margaret E Wright[a,*], **Gabriella Andreotti**[b], **Jolanta Lissowska**[c], **Meredith Yeager**[d], **Witold Zatonski**[c], **Stephen J Chanock**[d], **Wong-Ho Chow**[b], and **Lifang Hou**[e]

[a]Department of Pathology, College of Medicine, University of Illinois at Chicago, Chicago, IL, 60612, USA [b]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD, 20852, USA [c]Department of Cancer Epidemiology and Prevention, the M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, 02-781 Warsaw, Poland [d]Core Genotyping Facility, Advanced Technology Center, National Cancer Institute, NIH, DHHS, Gaithersburg, MD, 20892, USA [e]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, 60611, USA

Abstract

Higher ascorbic acid consumption is associated with a reduced risk of gastric cancer in numerous epidemiologic studies. We investigated whether single nucleotide polymorphisms (SNPs) in *SLC23A1* and *SLC23A2* — genes that encode key ascorbic acid transport proteins — affect gastric cancer risk in 279 incident cases and 414 age- and gender-matched controls drawn from a population-based case-control study in Poland. Compared to subjects who were homozygous for the common G allele of the *SLC23A2* SNP rs12479919, carriers of the AA genotype had a 41% lower risk of gastric cancer [odds ratio (OR) = 0.59, 95% confidence interval (CI): 0.36-0.95; *p* trend = 0.06]. A haplotype that contained the common allele of the rs6139591, rs2681116, and rs14147458 SNPs in *SLC23A2* was also significantly inversely associated with gastric malignancy. No other polymorphisms in either gene were related to risk, and there was no effect modification by ascorbic acid intake. These findings suggest that genetic variation in *SLC23A2* impacts gastric cancer risk, although confirmation in other studies is required.

Keywords

ascorbic acid; gastric cancer; single nucleotide polymorphism; susceptibility

Introduction

Gastric cancer is one of the most commonly diagnosed malignancies and the second leading cause of cancer-related deaths worldwide (1). Although gastric cancer incidence and mortality rates have been dropping in most European countries, considerable geographic variation in

*Corresponding author: Address: Department of Pathology, University of Illinois at Chicago, 840 S Wood St., CSN 130, Chicago, IL 60612, USA. Tel: +001 312 996 9684; fax: +001 312 996 4812. mewright@uic.edu.

Conflict of interest statement None declared.

these rates still exists, with the greatest burden observed in Southern and Central Europe (2). Furthermore, despite notable decreases in the incidence of gastric non-cardia tumors, the incidence of rarer cardia cancers appears to be increasing or remaining stable (2).

Nutritional factors appear to play an important role in the etiology of this disease: diets containing large amounts of smoked, salted, and pickled foods are linked to higher risk, whereas fruits and vegetables are linked to lower risk in numerous epidemiologic studies (3). The protective effects of fruit and vegetable consumption on risk of gastric and other cancers are largely ascribed to their high antioxidant nutrient concentrations. Ascorbic acid (vitamin C) is the primary water-soluble antioxidant found in fruits and vegetables, and is not only a powerful scavenger of reactive oxygen and nitrogen species, but also plays a crucial role in the synthesis of collagen, carnitine, and neurotransmitters (4). Recently, ascorbic acid was also shown to inhibit the growth of *Helicobacter pylori* — one of the most significant risk factors for gastric cancer (5).

Ascorbic acid concentrations in gastric mucosa and normal gastric juice are higher than those found in plasma, suggesting an important role for this micronutrient within the stomach (6-8). The sodium-dependent transporters SVCT1 and SVCT2 - encoded by the genes *SLC23A1* and *SLC23A2*, respectively — are directly responsible for intracellular accumulation of ascorbic acid, transporting it across membranes against a concentration gradient (9). While SVCT1 is localized primarily in epithelial tissues, SVCT2 has a much broader tissue distribution (10). Common single nucleotide polymorphisms (SNPs) have been identified in both genes (11), and could potentially alter the uptake and tissue distribution of ascorbate as well as related cancer risks.

No study to date has evaluated whether polymorphisms in genes that encode ascorbic acid transport proteins impact the risk of gastric cancer. We therefore examined whether variants in *SLC23A1* and *SLC23A2* were associated with incident gastric cancer risk in a population-based case-control study conducted in Warsaw, Poland, where the incidence of gastric cancer is high. We further evaluated whether these variants modified associations between gastric cancer risk and intake of ascorbic acid.

Materials and Methods

Study design

Data were derived from a population-based case-control study of gastric cancer that was carried out in Warsaw, Poland between 1994 and 1996. The study population has been described in detail previously (12). Incident cases of gastric cancer (ICD-O 151 or ICD-O-2 C16), ages 21-79 years, were identified between 1 March 1994 and 30 April 1996 by collaborating physicians in each of 22 hospitals serving the study area. Regular reviews of the Cancer Registry files ensured completeness of case ascertainment. All diagnoses were confirmed by study pathologists. Controls were selected at random using a computerized registry of all Warsaw residents and frequency matched to cases by sex and 5-year age groups. Written informed consent was obtained from all participants prior to interview. The study was approved by the Institutional Review Board of the U.S. National Cancer Institute (NCI) and the Cancer Center and M. Sklodowska-Curie Institute of Oncology, Warsaw, Poland.

Data collection

Trained interviewers collected detailed information on demographic characteristics, childhood living conditions, family history of cancer, medical history, occupational history, smoking history, and intake of alcohol and other beverages from cases (or next of kin of deceased cases) and controls. Usual diet prior to 1990 was assessed using a 118-item food-frequency

questionnaire, which was a modification of the Block questionnaire (13). Nutrient content of each food item was estimated using both U.S. and Polish food tables (14,15).

Of the 515 eligible cases and 549 eligible controls, 464 (90%) and 480 (87%) successfully completed interviews. Additionally, a 30 mL blood sample was collected from 345 cases (67.0%) and 442 controls (80.5%). Of these, genotyping results were available in 279 cases (54.2%) and 414 (75.4%) controls.

SNP selection and genotyping methods

Thirteen SNPs in the two genes of interest were identified by searching publicly available databases, including dbSNP (16) and NCI SNP500 (17). Priority was given to variants with potential functional significance, including those located in upstream promoters, coding regions, and exon-intron junctions. We also selected SNPs at regular intervals across each gene in order to enhance coverage.

Genotyping was conducted at the NCI Core Genotyping Facility using the TaqMan platform (sequence data and assay conditions can be found at http://snp500cancer.nci.nih.gov). Selected SNPs were verified in a panel of 102 reference samples from four ethnically diverse groups by resequencing approximately 300 base pairs of DNA on either side of the locus of interest. Genotyping assays were subsequently developed for known and newly discovered variants that exhibited a minor allele frequency >5% in Caucasians, and were considered to be validated when there was 100% concordance between sequence analysis and genotyping results on one or more of the aforementioned platforms. Genotyping success rates exceeded 97% for each of the SNPs.

Approximately 8% blind quality control samples from two individuals were interspersed with the study samples, which showed >99% concordance. All SNPs were in Hardy-Weinberg Equilibrium (HWE).

Statistical analysis

Differences in selected characteristics between gastric cancer cases and controls were compared using the Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables. Unconditional logistic regression was utilized to estimate odds ratios (OR) and 95% confidence intervals (CI) for gastric cancer risk in relation to each SNP, adjusted for age, sex, smoking status, pack-years of cigarette smoking, and education. The common homozygous genotype served as the reference group in each analysis, and tests for trend were conducted by first assigning values of 0, 1, and 2 to the homozygous wild-type, heterozygote, and homozygous variant genotypes, respectively, and then modelling these scores as a continuous variable. In alternative analyses, we imposed a dominant model of inheritance by comparing risk in the combined group of heterozygotes and homozygous rare genotypes to risk among the homozygous-common genotype.

We performed a global omnibus test for interaction for each gene with intake of ascorbic acid in relation to gastric cancer risk. Global tests were performed by simultaneously including all of the polymorphisms in a given gene (coded by two dummy variables corresponding to the homozygous and heterozygous variant genotypes), ascorbic acid intake (categorized according to the sex-specific US Recommended Dietary Allowances (18) as < 90, ≥ 90 mg/d for males and <75, ≥ 75 mg/d for females), and all cross-product terms in a logistic regression model and then comparing it to a null model containing only the main effects of the genotypes and ascorbic acid intake. These global tests automatically adjust for multiple testing based on the degrees of freedom of the corresponding likelihood-ratio test. Interactions between ascorbic acid intake

and individual variants and haplotypes demonstrating an association with gastric cancer risk were also evaluated using likelihood ratio tests.

Pair-wise measures of linkage disequilibrium (Lewontin's D' and r^2) were calculated among controls between polymorphic loci in the same gene using Haploview version 4.1 (19). Haplotype frequencies, ORs, and 95% CIs were estimated using HaploStats in R (http://mayoresearch.mayo.edu/mayo/research/biostat/schaid.cfm), which reconstructs haplotypes using an Expectation-Maximization algorithm to calculate maximum likelihood estimates of haplotype frequencies while taking into account phase ambiguity (20,21). Associations between haplotypes (>5% frequency) and gastric cancer were evaluated using the most common haplotype as the referent category. Global differences in haplotype frequencies between cases and controls were assessed for each gene using the Score test in Haplostats.

Statistical analyses were performed using Statistical Analysis Systems (SAS) software, version 8.02 (SAS Inc., Cary, NC). All tests were two-sided at the 0.05 significance level.

Results

As expected, cases and controls did not differ with respect to age at enrolment or gender distribution, both of which were matching variables (Table 1). On the other hand, cases were less well-educated and more likely to be a current smoker, heavier drinker, and to report a first-degree family history of gastric cancer than controls. With respect to dietary intake, cases consumed fewer servings of fruit and juices per week than controls did; no differences were noted, however, for intakes of total vegetables, raw vegetables, ascorbic acid, and calories. The majority of gastric cancers were of the intestinal histologic type (68%), and most originated in the distal stomach (73%).

Among the 13 SNPs examined, only one — *SLC23A2* IVS2+1312 G>A — was significantly inversely associated with gastric cancer risk (Table 2). Compared to carriers of both copies of the common allele, carriage of one or two copies of the minor A allele was associated with a lower risk of gastric cancer [ORs and 95% CIs = 0.75 (0.53-1.06) and 0.59 (0.36-0.94), respectively; *P* trend = 0.06]. One other SNP in *SLC23A2* (EX12+57 T>C) was associated with a borderline significant reduction in gastric cancer risk; participants who were homozygous for the minor allele had an approximate 45% reduction in risk compared to carries of both copies of the common allele [OR = 0.56, 95% CI: 0.30-1.04] (Table 2). None of the variants in *SLC23A1* were associated with gastric cancer risk.

Of the nine *SLC23A2* SNPs examined, strong LD (D' between 0.9 and 1.0) was present among controls for three of the SNPs (IVS3+80 C>T, IVS3+108 A>G, and IVS3+224 T>G). We inferred three major haplotypes (frequency ≥5%) from these three high LD SNPs among controls (CAT: 47%, TGG: 36%, CGT: 13%). The CGT haplotype, which contained the common allele for each of the three SNPS, was associated with a decreased risk of gastric cancer compared with the most frequent haplotype (CAT) [OR=0.65, 95% CI: 0.45-0.92] (Table 2). The global test for difference in *SLC23A2* haplotype frequencies between cases and controls was not statistically significant (*P*=0.11). Strong LD (D' 0.92) was also present among controls for -81253 C>A and IVS2+1312 G>A (the marker which was associated with gastric cancer). We inferred three major haplotypes from these two SNPs among controls (CG: 41%, CA: 40%, AG: 19%), but found no significant associations with gastric cancer risk (data not shown). No significant associations were observed for the *SLC23A1* haplotypes.

Global omnibus tests showed no statistically significant effect modification of the relation between overall variation in each gene and gastric cancer risk by dietary intakes of ascorbic acid (all *P*-values > 0.05). There was also no interaction observed between ascorbic acid intake

and the individual *SLC23A2* IVS2+1312 G>A and EX12+57 T>C polymorphisms nor haplotypes.

Discussion

No previous study has examined whether genetic variation in the sodium-dependent ascorbic acid transporters, *SLC23A1* and *SLC23A2*, is associated with gastric malignancy. We found that one intronic SNP (IVS2+1312 G>A), as well as a haplotype that contained the common allele of the IVS3+80 C>T, IVS3+108 A>G, and IVS3+224 T>G markers, in *SLC23A2* were significantly inversely associated with gastric cancer risk. We observed no relation between variants in *SLC23A1* and disease. This is somewhat surprising considering the greater observed diversity in *SLC23A1* compared to *SLC23A2* (11). However, SVCT2 (the protein product of *SLC23A2*) but not SVCT1 (the protein product of *SLC23A1*) has been detected in gastric glands from rats, implicating *SLC23A2* as the primary means of ascorbic acid uptake in this organ (10).

Our hypothesis that common genetic variation in *SLC23A1* and *SLC23A2* could impact gastric cancer risk is based on strong biological evidence that ascorbic acid plays an important role in the stomach. Fresh fruit and vegetables — the primary sources of ascorbic acid — have been linked to a lower risk of gastric cancer in many epidemiologic studies, including our own (3, 22). These foods contain a plethora of potentially anti-carcinogenic substances (23), but of all the compounds that have been examined thus far, ascorbic acid has been the most consistently inversely associated with gastric cancer risk (24). Paradoxically, not all ascorbic acid supplementation trials support these conclusions (25), and reasons for discrepancies between observational studies and randomized trials include differences in dose, duration, and timing of the intervention (26). In our study population, ascorbic acid supplementation was uncommon and approximately 65% of male and female control subjects had ascorbic acid intake below the current recommended level of intake in the US (18). We found that the associations with the *SLC23A2* haplotypes, and specifically the IVS2+1312 G>A polymorphism, were not modified by adequate versus deficient levels of ascorbic acid intake. However, we were unable to examine whether the bioavailability of ascorbic acid in our study subjects was related to their genetic variation in sodium-dependent ascorbic acid transporters for lack of appropriate biological samples.

Ascorbic acid is highly concentrated in gastric mucosa and gastric juice and individuals with chronic gastritis or overt cancer have substantially lower concentrations than their healthier counterparts, suggesting a particularly important role(s) for this micronutrient in the etiology of gastric cancer (6-8). In addition to its ability to neutralize reactive oxygen species and inhibit the formation of N-nitroso compounds in the stomach (27-29), studies have shown that ascorbic acid can inhibit cell proliferation and induce apoptosis in gastric cells (30). Furthermore, ascorbic acid appears to directly affect *H. pylori* growth and virulence (5,31).

Strengths of this study include its population-based design, high participation rates among cases and controls, availability of detailed dietary information, the ability to control for multiple confounders, and high reproducibility of genotyping. A limitation is our evaluation of only publicly available SNPs rather than resequencing the functional domains of each gene in order to more comprehensively identify other variants. We also could not assess the functionality of the selected polymorphisms, as serum ascorbic acid levels were not available. These are critical areas of ongoing research. Another possible limitation is selection bias since a blood sample was not obtained from all participants; however, there were no apparent differences in demographic and lifestyle characteristics between cases with and without DNA samples. The case-control study design is also susceptible to recall bias, but this has no effect on genotype associations.

In summary, we show that common variants in *SLC23A2*, a gene that directly regulates active transport of ascorbic acid, can impact gastric cancer risk. Confirmation of our findings in other studies is required, as is continued functional characterization of polymorphisms in this and other related genes.

Acknowledgements

This study was supported, in part, by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics.

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Table 1

Selected characteristics of gastric cancer cases and controls

	Cases (*n*=279)	Controls (*n*=414)	*p*-value[a]
	***n* (%)**	***n* (%)**	
Age (years)			0.96
≤50	34 (12.2)	51 (12.3)	
50-59	51 (18.3)	72 (17.4)	
60-69	113 (40.5)	163 (39.4)	
≤70	81 (29.0)	128 (30.9)	
Gender			0.65
Male	186 (66.7)	269 (65.0)	
Female	93 (33.3)	145 (35.0)	
Education			0.002
≤ High school	133 (47.7)	157 (37.9)	
Some college	96 (34.4)	137 (33.1)	
≥ College graduate	50 (17.9)	120 (29.0)	
Smoking status			0.0002
Never	78 (28)	167 (40.3)	
Former	84 (30.1)	132 (31.9)	
Current	115 (41.2)	115 (27.8)	
Family history of cancer			0.0002
None	161 (57.7)	274 (66.2)	
Gastric cancer	34 (12.2)	17 (4.11)	
Other cancer	73 (26.2)	116 (28.0)	
Unknown	11 (3.9)	7 (1.7)	
Tumour localization			
Cardia only	32 (11.5)	N/A[b]	
Distal stomach	203 (72.8)	N/A	
Combined cardia / distal	34 (12.2)	N/A	
Unknown	10 (3.6)	N/A	
Lauren classification[c]			
Intestinal	182 (67.9)	N/A	
Diffuse	49 (18.3)	N/A	
Indeterminate	32 (11.9)	N/A	
Unknown	5 (1.9)	N/A	
	Mean (SD)	**Mean (SD)**	
Pack-years of smoking	35.9 (104)	20.7 (53.5)	0.03
Alcohol consumption, drinks/week[d]	6.0 (15.4)	3.3 (6.2)	0.006
Dietary intake[e]			
Calories, kcal/day	2859 (824)	2821 (793)	0.57

	Cases (*n*=279)	Controls (*n*=414)	*p*-value[a]
	***n* (%)**	***n* (%)**	
Fruits and juices, freq/week	4.5 (3.5)	5.6 (4.2)	0.0005
Vegetables, freq/week	21.6 (7.3)	22.5 (8.3)	0.17
Raw vegetables, freq/week	5.7 (4.1)	6.1 (4.1)	0.21
Ascorbic acid, mg/day	77 (35.4)	81.1 (37.5)	0.17

[a] Based on the χ^2 test for categorical variables and t-test for continuous variables

[b] N/A = not applicable

[c] Information available for 268 cases

[d] Information available for 276 cases and 412 controls

[e] Information available for 234 cases and 401 controls

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for gastric cancer risk according to *SLC23A1* and *SLC23A2* genotypes and haplotypes

	Cases (*n*=279)	Controls (*n*=414)	OR[a] (95% CI)
SLC23A1			
-583 G>A (rs10063949)			
AA	137	209	1.00
GA	115	169	1.04 (0.75-1.45)
GG	23	33	1.11 (0.62-2.01)
P trend			0.93
G-carrier	138	202	1.05 (0.77-1.44)
IVS9-101 C>T (rs11950646)			
TT	137	209	1.00
CT	112	167	1.02 (0.74-1.42)
CC	26	35	1.19 (0.68-2.10)
P trend			0.83
C-carrier	138	202	1.05 (0.77-1.44)
IVS10+109 C>T (rs4257763)			
TT	137	206	1.00
CT	118	169	1.05 (0.76-1.46)
CC	23	34	1.08 (0.60-1.94)
P trend			0.94
C-carrier	141	203	1.06 (0.77-1.44)
IVS13+2515 C>G (rs6596473)			
CC	141	218	1.00
CG	117	164	1.12 (0.81-1.55)
GG	20	31	1.06 (0.57-1.97)
P trend			0.81
G-carrier	137	195	1.11 (0.81-1.51)
Haplotypes			
A-T-T-C	71%	70%	1.00
G-C-C-G	27%	27%	0.99 (0.75-1.29)
Global *P*			0.87
SLC23A2			
-81253 C>A (rs6053034)			
CC	174	273	1.00
CA	86	125	1.07 (0.76-1.50)
AA	13	13	1.46 (0.65-3.28)
P trend			0.64
A-carrier	99	138	1.11 (0.80-1.54)
IVS2+1312 G>A (rs12479919)			
GG	112	133	1.00
AG	125	202	0.75 (0.53-1.06)

	Cases (*n*=279)	Controls (*n*=414)	OR[a] (95% CI)
AA	39	75	0.59 (0.36-0.94)
P trend			0.06
A-carrier	164	277	0.71 (0.51-0.98)
IVS2+14050 C>A (rs2681118)			
AA	163	263	1.00
AC	97	128	1.23 (0.88-1.72)
CC	13	19	1.03 (0.49-2.18)
P trend			0.49
C-carrier	110	147	1.20 (0.87-1.66)
IVS3+80 C>T (rs6139591)			
CC	123	167	1.00
CT	115	182	0.89 (0.63-1.25)
TT	38	57	1.00 (0.61-1.62)
P trend			0.76
T-carrier	153	239	0.91 (0.66-1.25)
IVS3+108 A>G (rs2681116)			
GG	64	110	1.00
AG	136	207	1.09 (0.74-1.60)
AA	71	90	1.36 (0.87-2.14)
P trend			0.37
A-carrier	207	297	1.17 (0.81-1.68)
IVS3+224 T>G (rs13037458)			
TT	120	164	1.00
GT	112	182	0.87 (0.62-1.22)
GG	38	57	0.99 (0.61-1.61)
P trend			0.70
G-carrier	150	239	0.90 (0.65-1.24)
IVS3-4623 G>A (rsrs4813725)			
GG	98	148	1.00
AG	130	202	0.98 (0.69-1.39)
AA	45	56	1.29 (0.80-2.09)
P trend			0.48
A-carrier	175	258	1.05 (0.75-1.45)
Ex7+51 C>T A125A (rs1776964)			
TT	79	114	1.00
CT	146	199	1.04 (0.72-1.50)
CC	51	99	0.75 (0.48-1.18)
P trend			0.29
C-carrier	197	298	0.94 (0.67-1.33)
Ex12+57 T>C D334D (rs1110277)			
TT	153	206	1.00

	Cases (*n*=279)	Controls (*n*=414)	OR[a] (95% CI)
CT	106	162	0.88 (0.63-1.23)
CC	17	39	0.56 (0.30-1.04)
P trend			0.18
C-carrier	123	201	0.82 (0.60-1.12)
Haplotypes[b]			
C-A-T	52%	47%	1.00
T-G-G	35%	36%	0.89 (0.69-1.15)
C-G-T	17%	13%	0.65 (0.45-0.92)
Global *P*			0.11

[a] Adjusted for age, sex, education, and smoking

[b] Based on 3 SNPs in the following order within the identified block: IVS3+80 C>T, IVS3+108 A>G, and IVS3+224 T>G