Vitamin C Transporter Gene Polymorphisms, Dietary Vitamin C and Serum Ascorbic Acid

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Abstract

Background/Aims: Vitamin C transporter proteins SVCT1 and SVCT2 are required for the absorption and transport of vitamin C in humans. This study aims to determine whether common SVCT genotypes modify the association between dietary vitamin C and serum ascorbic acid. Methods: Non-smoking men and women (n = 1,046) aged 20–29 were participants of the Toronto Nutrigenomics and Health Study. Overnight fasting blood samples were collected to determine serum ascorbic acid concentrations by HPLC and to genotype for two SVCT1 (rs4257763 and rs6596473) and two SVCT2 (rs6139591 and rs2681116) polymorphisms. Results: No diet-gene interactions were observed for the vitamin C transporter polymorphisms, however, the average (mean ± SE) serum ascorbic acid concentrations differed between rs4257763 genotypes (GG: 24.4 ± 1.3, GA: 26.8 ± 1.1, AA: 29.7 ± 1.4 μmol/l; p = 0.002). For this polymorphism, the correlation between dietary vitamin C and serum ascorbic acid was only significant in subjects with a G allele. The SVCT2 polymorphisms also appeared to modify the strength of the diet-serum correlation. Conclusions: Our findings demonstrate that genetic variation in SVCT1 can influence serum ascorbic acid concentrations and that SVCT1 and SVCT2 genotypes modify the strength of the correlation between dietary vitamin C and serum ascorbic acid.

Introduction

Ascorbic acid (vitamin C) plays important physiological roles in the human body as a reducing agent, a free radical scavenger, and enzyme cofactor required for the synthesis of carnitine, collagen, norepinephrine and epinephrine. Recent reports have revealed that deficient serum ascorbic acid concentrations are common, occurring in 8–16% of young North American adults [1, 2]. Furthermore, serum ascorbic acid concentrations are inversely associated with markers of chronic disease such as BMI, high sensitivity C-reactive protein (hs-CRP) and blood pressure in young adults [2, 3]. In older adults, an...
inverse relationship exists between serum ascorbic acid concentrations and risk of cardiovascular disease [4, 5], diabetes [6, 7], some forms of cancer [8] and all-cause mortality [9].

There is substantial variability in the serum ascorbic acid response to a given amount of dietary vitamin C [10], even when controlling for known determinants of serum ascorbic acid such as age [11], sex [12, 13], smoking [12, 14], body weight [10, 15], physical activity [16] and season [14]. Genetic variation can also explain some of the individual variability observed in serum ascorbic acid response to dietary vitamin C, with the common haptoglobin polymorphism [17, 18], and glutathione-S-transferase deletion polymorphisms [19, 20], influencing serum ascorbic acid concentrations. However, these polymorphisms do not explain all of the individual variability observed in serum ascorbic acid concentrations, and other genes might also be involved.

Sodium-dependent vitamin C transporter 1 (SVCT1), encoded by the SLC23A1 gene, is required for intestinal absorption and renal reabsorption of vitamin C in humans and is also expressed in the skin, liver and lungs [21]. SVCT2 is encoded by the SLC23A2 gene and functions to transport vitamin C into other tissues and cells (including eye, brain, bone, heart, adrenal gland and skeletal muscle) [21]. Common polymorphisms have recently been identified in the SLC23A1 and SLC23A2 genes [22]. Recent studies have reported an effect of SVCT polymorphisms on risk of preterm birth [23], colorectal adenoma [24], HPV16-associated head and neck cancer [25], several types of lymphoma [26], and gastric cancer [27], which are all health outcomes that have been associated with low vitamin C [28–32]. However, no studies to date have examined the effects of genetic variations in the vitamin C transporters on serum ascorbic acid concentrations. The purpose of this study was to determine whether polymorphisms of SVCT1 and SVCT2 influence fasting serum ascorbic acid concentrations and modify the association between dietary vitamin C and serum ascorbic acid.

Subjects and Methods

Study Design and Population

Subjects were women (n = 886) and men and (n = 391) aged 20–29 years who were recruited from the University of Toronto campus to be participants in the Toronto Nutrigenomics and Health Study. This cross-sectional study involved the collection of blood, anthropometrics, dietary intake and lifestyle information. All subjects provided written informed consent. The study protocol was approved by the Research Ethics Board at the University of Toronto.

Individuals did not participate in the study if they could not provide a venous blood sample or if they were pregnant or breastfeeding. Smokers (n = 88) were excluded because of the known ascorbic acid-depleting effects of smoking [12, 14]. Individuals who may have under-reported (<800 kcal/day) or over-reported (>3,500 kcal/day for women, >4,000 kcal/day for men) their energy intakes (n = 93) were excluded. Subjects were also excluded if they had any missing data (n = 50). After exclusions, 1,046 subjects (737 women and 309 men) remained. Vitamin C supplement users (n = 383) were identified as anyone who took a vitamin C-containing multivitamin (n = 218), a supplement containing vitamin C exclusively (n = 76), or both (n = 89). Three major ethnic-cultural groups were present within the sample: Caucasian (n = 496), East Asian (n = 366) and others (n = 184), which included those with a mix of two or more ethnic-cultural groups. The date when each subject provided the blood sample was used to classify the subjects by the four seasons: spring (March–May), summer (June–August), autumn (September–November) and winter (December–February).

Serum Ascorbic Acid

Overnight 12-hour fasting blood samples were collected at LifeLabs medical Laboratory Services (Toronto, Ont., Canada), where all of the biochemical measures were performed. Serum ascorbic acid concentrations were measured as previously described using high-performance liquid chromatography [2, 20]. Briefly, salicylic acid was used as a deproteinizing agent, metaphosphoric acid as a stabilizer and amber tubes were used to prevent photodegradation. Samples were stored at −20°C for less than 6 days, and plasma ascorbic acid has been shown to be stable under these conditions [33, 34]. Certified controls from the National Institute of Standards and Technology (NIST) were used to ensure the validity of the method [35]. A control sample from NIST was run after calibrating and after every tenth sample analyzed, and the observed CV ranged from 4.9–7.8%.

Genotyping

The overnight 12-hour fasting blood samples also provided the DNA (isolated from peripheral white blood cells) used to genotype all subjects for four SVCT1 and SVCT2 polymorphisms. Applied Biosystems SNP assays and real-time polymerase chain reaction were used to determine the genotypes of subjects for two SVCT1 polymorphisms (rs4257763 and rs6596473) and two SVCT2 polymorphisms (rs6139591 and rs2681116) in all subjects. Controls and a random 5% replication of samples were included alongside samples and complete concordance was observed. The names and alleles of the SNPs are as per dbSNP [36].

Although rs4257763 and rs6596473 SNPs in SVCT1 may be inherited together, their linkage disequilibrium is not complete, and the same is true for the two SVCT2 SNPs [23].

Dietary Assessment

Subjects completed a 196-item Toronto-Modified Willett Food Frequency Questionnaire (FFQ), which estimated their daily dietary intake of vitamin C-containing foods and supplements as well as other dietary habits during the last month. In the FFQ, subjects were offered nine possible responses to indicate how many times in the past month they consumed a specified portion
of each food: never, less than once per month, 1–3 times per month, once per week, 2–4 times per week, 5–6 times per week, once per day, 2–3 times per day, and 4 or more times per day. Subject responses to the individual foods were converted to average daily intake for each item. The average daily intakes of all items were combined to compute a total daily dietary vitamin C for each subject.

Statistical Analysis

Analyses were performed using Statistical Analysis Systems software (SAS version 9.1; SAS Institute Inc., Cary, N.C., USA). Significant p values were two-sided and <0.05. Departure from Hardy-Weinberg equilibrium was assessed by comparing the genotype distributions using \(\chi^2\) tests with 1 d.f. Subject characteristics were compared between genotypes using \(\chi^2\) tests for categorical variables and a general linear model for continuous variables with a Bonferroni correction for multiple comparisons (p < 0.0167). p values from log-transformed analyses are displayed for BMI, waist circumference, total:HDL cholesterol ratio, hs-CRP, and dietary vitamin C, as these variables were skewed. Potential gene-diet interactions were evaluated using a general linear model because the dependent variable (serum ascorbic acid) had a normal distribution. Covariate-adjusted mean serum ascorbic acid concentrations were compared between genotypes in an analysis of variance. Statistical analyses were conducted for the polymorphism individually and then in combination with the SVCT1 SNPs together and the SVCT2 SNPs together, because some previous studies have presented results for these vitamin C transporter SNPs together and the SVCT2 SNPs together, because some previous studies have presented results for these vitamin C transporter SNPs which have incomplete linkage disequilibrium within each gene as haplotypes [23, 27]. The Pearson correlation test with stratification by genotype was used to examine the correlations between dietary vitamin C and serum ascorbic acid concentrations as continuous variables for the different genotypes.

The adjusted model used in the analyses included sex, BMI, ethnocultural group, hs-CRP, \(\alpha\)-tocopherol, oral contraceptive use (women only) and season, as determined by stepwise linear regression and an analysis of covariance at a 0.05 significance level. Energy intake was included in the model of analyses with dietary vitamin C. No interactions between these covariates and dietary vitamin C on serum ascorbic acid concentrations were observed. A number of other covariates were considered as potential confounders, including age, intake of carotenoids, flavonoids, iron, fiber and alcohol, supplement use, serum lipids, blood pressure and physical activity. However, none was statistically significant or materially altered the results and so these variables were not included in the final model.

Results

Genotype frequencies and subject characteristics are summarized in table 1 (SVCT1) and table 2 (SVCT2). Genotype frequencies for all of the polymorphisms were in Hardy-Weinberg equilibrium within each major ethnocultural group. No subject characteristics differed among the SVCT2 rs6139591 genotypes, and the only subject characteristics to differ among the SVCT2 rs2681116 genotypes were ethnocultural group and hscrp. However, a considerable number of subject characteristics differed among the SVCT1 genotypes, including age, ethnocultural group, BMI, waist circumference, oral contraceptive use, blood pressure and hs-CRP. These differences are likely due to population admixture because a larger proportion of Caucasians than East Asians have the rs4257763 A allele and the rs6596473 G allele, and the Caucasians in this population have a higher BMI, waist circumference, age, hs-CRP and blood pressure than the East Asians. Indeed, these parameters were no longer different between the genotypes when stratified by ethnocultural group or adjusted in a fitted model that includes ethnocultural group (data not shown). Similarly, the difference in dietary vitamin C for the rs4257763 genotype and the difference in hs-CRP for the rs2681116 genotype no longer exist when the adjusted model is used (data not shown). No interactions between BMI, waist circumference, hs-CRP, blood pressure, ethnocultural group or dietary vitamin C and the polymorphisms on serum ascorbic acid were observed.

Serum ascorbic acid was the only variable that remained significantly different between the genotypes when the adjusted model was used (table 3). Average serum ascorbic acid concentrations (\(\mu\)mol/l, mean ± SE) were lower in individuals with the GG genotype (24.4 ± 1.3) than the AA (29.7 ± 1.4) genotype, with the GA group (26.8 ± 1.1) being intermediate, for the SVCT1 rs4257763 polymorphism (Bonferroni correction p < 0.0167). This difference was also significant in Caucasian subjects (GG: 25.6 ± 2.1, GA: 27.3 ± 1.3, AA: 30.9 ± 1.3), but not in East Asians, possibly because of the smaller sample size, although the trend (p = 0.14) was in the same direction (GG: 26.2 ± 1.9, GA: 29.5 ± 2.1, AA: 30.1 ± 3.6). The association between serum ascorbic acid concentration and the SVCT1 rs4257763 polymorphism was independent of supplement use (data not shown). Mean adjusted serum ascorbic acid concentrations were not significantly different between SVCT1 rs6596473 genotypes. However, when combined with the rs4257763 SNP, serum ascorbic acid concentrations did differ among the combinations, which represent common haplotypes as presented in table 3. Subjects with the combination of the rs4257763 AA and the rs6596473 GG genotypes had the highest serum ascorbic acid concentrations (29.4 ± 1.4), while subjects with the rs4257763 GG and the rs6596473 GC genotype combination had the lowest serum ascorbic acid (20.6 ± 2.2) (p = 0.003). Average adjusted serum ascorbic acid concentrations did not vary...
between the genotypes of the two SVCT2 polymorphisms when analyzed separately or combined (data not shown).

The crude and adjusted correlations between dietary vitamin C and serum ascorbic acid for the different genotypes are presented in Table 4. For the SVCT1 rs4257763 polymorphism, adjusted correlations were only significant in subjects with the GG or GA genotypes and not the AA genotype. Correlations were significant for all genotypes of the SVCT1 rs6596473 SNP, but appeared strongest in subjects with the CC genotype. For the SVCT2 polymorphisms, the GG genotype of the rs6139591 SNP and the TT genotype of the rs2681116 SNP appear to have the strongest correlation between dietary vitamin C and serum ascorbic acid.
Discussion

The purpose of the present study was to determine whether common vitamin C transporter polymorphisms modify the association between dietary vitamin C and serum ascorbic acid. We observed that one common polymorphism in the SLC23A1 gene affects concentrations of fasting serum ascorbic acid independent of diet in a young and healthy population. Because no diet-gene interactions were present, the slopes of the genotypes did not differ, and it cannot be concluded that the SVCT1 and SVCT2 genotypes modify the serum ascorbic acid response to dietary vitamin C. However, correlation coefficients did appear to differ between the genotypes, indicating that the polymorphisms may alter the strength of the diet-serum association for vitamin C and should be
Table 3. Adjusted mean serum ascorbic acid values for SVCT1 genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>All subjects</th>
<th>Caucasians</th>
<th>East Asians</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean ± SE</td>
<td>p</td>
</tr>
<tr>
<td>rs4257763</td>
<td>GG</td>
<td>318</td>
<td>24.4 ± 1.3a</td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>462</td>
<td>26.8 ± 1.1a,b</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>266</td>
<td>29.7 ± 1.4b</td>
</tr>
<tr>
<td>rs6596473</td>
<td>GG</td>
<td>301</td>
<td>28.6 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>GC</td>
<td>490</td>
<td>26.1 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>255</td>
<td>25.7 ± 1.4</td>
</tr>
<tr>
<td>rs4257763 + rs6596473*</td>
<td>AA + GG</td>
<td>253</td>
<td>29.4 ± 1.4a</td>
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<tr>
<td></td>
<td>GA + GC</td>
<td>416</td>
<td>26.8 ± 1.1a</td>
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<tr>
<td></td>
<td>GG + CC</td>
<td>246</td>
<td>25.5 ± 1.4a,b</td>
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<tr>
<td></td>
<td>GG + GC</td>
<td>64</td>
<td>20.6 ± 2.2b</td>
</tr>
</tbody>
</table>

* Genotype combinations with fewer than 40 individuals are not shown. Model adjusted for sex, plasma α-tocopherol, ethnocultural group, BMI, season, hs-CRP, and oral contraceptive use (women only). Values with different superscripts are significantly different following a Bonferroni correction for multiple comparisons (p < 0.0167). No diet-gene interactions were observed.

Table 4. Pearson correlation coefficients between dietary vitamin C and serum ascorbic acid by SVCT genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n</th>
<th>SVCT1</th>
<th></th>
<th></th>
<th></th>
<th>SVCT2</th>
<th></th>
<th></th>
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<tbody>
<tr>
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<td>0.21b</td>
<td>0.16b</td>
<td>0.17b</td>
<td>0.21b</td>
<td>0.16b</td>
<td>0.19b</td>
<td>0.23c</td>
<td>0.15b</td>
<td>0.18a</td>
<td>0.14a</td>
<td>0.19c</td>
</tr>
<tr>
<td>rs6596473 (n)</td>
<td>663</td>
<td>0.13a</td>
<td>0.20b</td>
<td>0.16a</td>
<td>0.24b</td>
<td>0.15b</td>
<td>0.13</td>
<td>0.22b</td>
<td>0.16b</td>
<td>0.12</td>
<td>0.15a</td>
<td>0.16b</td>
</tr>
<tr>
<td>rs6139591 (n)</td>
<td>391</td>
<td>0.32b</td>
<td>0.33c</td>
<td>0.16</td>
<td>0.26a</td>
<td>0.29b</td>
<td>0.39b</td>
<td>0.46c</td>
<td>0.22b</td>
<td>0.30b</td>
<td>0.30b</td>
<td>0.24b</td>
</tr>
<tr>
<td>rs2681116 (n)</td>
<td>886</td>
<td>0.18b</td>
<td>0.08</td>
<td>0.16b</td>
<td>0.18b</td>
<td>0.10</td>
<td>0.15a</td>
<td>0.16b</td>
<td>0.11a</td>
<td>0.14</td>
<td>0.09</td>
<td>0.17b</td>
</tr>
<tr>
<td></td>
<td>496</td>
<td>0.17</td>
<td>0.15a</td>
<td>0.17a</td>
<td>0.20b</td>
<td>0.12</td>
<td>0.21</td>
<td>0.22b</td>
<td>0.16b</td>
<td>0.04</td>
<td>0.02</td>
<td>0.23b</td>
</tr>
<tr>
<td></td>
<td>366</td>
<td>0.21b</td>
<td>0.14</td>
<td>0.06</td>
<td>0.01</td>
<td>0.24b</td>
<td>0.19b</td>
<td>0.19a</td>
<td>0.19a</td>
<td>0.24</td>
<td>0.17</td>
<td>0.23b</td>
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Model 1

<table>
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<th>Genotype</th>
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<th>SVCT1</th>
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<th></th>
<th></th>
<th>SVCT2</th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
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<td>rs4257763 (n)</td>
<td>1,046</td>
<td>0.22b</td>
<td>0.12a</td>
<td>0.11</td>
<td>0.17b</td>
<td>0.13b</td>
<td>0.20b</td>
<td>0.21c</td>
<td>0.12b</td>
<td>0.16</td>
<td>0.15a</td>
<td>0.15b</td>
</tr>
<tr>
<td>rs6596473 (n)</td>
<td>663</td>
<td>0.25b</td>
<td>0.18b</td>
<td>0.07</td>
<td>0.21b</td>
<td>0.14a</td>
<td>0.26b</td>
<td>0.25b</td>
<td>0.19b</td>
<td>0.13</td>
<td>0.18a</td>
<td>0.20b</td>
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<tr>
<td>rs6139591 (n)</td>
<td>391</td>
<td>0.34b</td>
<td>0.28b</td>
<td>0.11</td>
<td>0.22a</td>
<td>0.24b</td>
<td>0.37b</td>
<td>0.42c</td>
<td>0.20a</td>
<td>0.25</td>
<td>0.30b</td>
<td>0.19a</td>
</tr>
<tr>
<td>rs2681116 (n)</td>
<td>886</td>
<td>0.20b</td>
<td>0.04</td>
<td>0.11</td>
<td>0.15a</td>
<td>0.08</td>
<td>0.17b</td>
<td>0.17b</td>
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<td>0.13a</td>
<td>0.15a</td>
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<tr>
<td></td>
<td>496</td>
<td>0.10</td>
<td>0.10</td>
<td>0.10</td>
<td>0.14a</td>
<td>0.06</td>
<td>0.14</td>
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<td>0.10</td>
<td>0.03</td>
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<td>0.22b</td>
<td>0.21a</td>
<td>0.19a</td>
<td>0.19a</td>
<td>0.20</td>
<td>0.19</td>
<td>0.23b</td>
</tr>
</tbody>
</table>

a p < 0.05, b p < 0.01, c p < 0.0001.

Model 1 is unadjusted. Model 2 is adjusted for sex, plasma α-tocopherol, energy intake, ethnocultural group, BMI, season, hs-CRP, and oral contraceptive use (women only). The dietary vitamin C variable is log-transformed. Supplement use includes the use of vitamin C supplements and vitamin C-containing multivitamins. No interactions were observed between dietary vitamin C interactions and sex (p = 0.19), supplement use (p = 0.08), or ethnocultural group (p = 0.97) on serum ascorbic acid.
considered in future studies that examine modifiers of the effects of vitamin C.

Genotype frequencies for all four SNPs reported in the present study are comparable to frequencies reported in other populations for Caucasians [24] and Asians [36]. The difference in serum ascorbic acid concentrations between SVCT1 rs4257763 genotypes that was observed among all study participants together was also significant among Caucasians alone, although not among East Asians, which is likely due to the smaller sample size of East Asian subjects.

Using data from the Pregnancy, Infection and Nutrition Study (1995–2000), Erichsen et al. [23] have linked common genetic variants in both SVCT1 and SVCT2 to spontaneous preterm birth via the role of vitamin C in producing collagen that prevents premature membrane ruptures through maintaining tensile membrane strength. This study did not include serum ascorbic acid concentrations, however, potential differences among genotypes in risk of spontaneous preterm birth were found for the SVCT1 haplotype that includes rs4257763 and rs6596473, and for rs6139591 and rs2681116 in SVCT2 SNPs, thus providing the rationale for the SNP selection in the present study. The most striking finding was for the rs6139591 polymorphism in the SVCT2 gene, as mothers homozygous for the A allele had a 2.7-fold (95% CI 1.2–6.3) increased risk of spontaneous preterm birth compared to mothers homozygous for the G allele [23]. A potential beneficial association of reduced risk of spontaneous preterm birth was linked with the haplotype containing the G allele for the rs4257763 polymorphism and the C allele for rs6596473, the G allele for rs6139591 and the T allele for rs2681116 [23]. In the present study, these same alleles were associated with the genotypes for which the correlations between dietary vitamin C and serum ascorbic acid were found to be the strongest and most significant. It is plausible that the beneficial genotypes in the preterm birth study might be associated with the strongest diet-serum correlation because more serum ascorbic acid could be available to be used in collagen formation. In the present study, the results for the rs4257763 SNP in SVCT1 (expressed in the kidneys) can be explained if the AA genotype is more efficient at reabsorbing ascorbic acid in the kidneys, which would otherwise be excreted.

A few other studies have investigated the health outcomes of genetic variants in the vitamin C transporters, but the results have been equivocal. In a study of 146 genes investigated for susceptibility to lymphoma, SLC23A1 and SLC23A2 were among the few that were associated with risk [26]. The SVCT1 rs6596473 CC genotype had a significantly higher risk of follicular lymphoma than the GG genotypes, but this study did not genotype for rs4257763, the other SVCT1 SNP investigated in the present study, which is the SNP we observed to be a genetic determinant of fasting serum ascorbic acid concentrations. In the present study, no effect of the rs6596473 SNP alone on serum ascorbic acid concentrations was seen, however, in combination with rs4257763, an effect was observed. Perhaps, the lesser risk of lymphoma experienced by the rs6596473 GG genotypes as compared to the CC genotype in the study of Skibola et al. [26] can be explained by higher serum ascorbic acid concentrations in many GG genotype individuals due to linkage disequilibrium with the rs4257763 AA genotype. However, this follicular lymphoma association was only seen in the American, and not the German population studied [26]. A case-control study of gastric cancer in Poland found no associations with SVCT1, but a reduced risk of gastric cancer with the combination of the SVCT2 SNPs (the A allele for rs6139591 and the C allele for rs2681116) [27]. No associations were observed between common haplotypes in SLC23A1 or single genotypes in SLC23A1 or SLC23A2 and advanced colorectal adenoma after analysis of 656 Caucasian advanced distal colorectal adenoma cases and 665 Caucasian controls from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial [24]. A reduced risk of advanced colorectal adenoma was observed for one relatively rare (1% of Caucasian subjects) haplotype in SLC23A2 [24]. A study that did not genotype for the 4 SNPs in the present study reported an interaction between citrus fruit intake and a SNP (rs4987219) in the SVCT2 gene on risk of HPV16-associated head and neck cancer [25]. SVCT1 and SVCT2 are regulated by their own substrate, ascorbic acid, as elevated ascorbic acid levels can decrease intestinal SVCT1 expression and SVCT2-mediated cellular uptake in other compartments [21].

The dominant mechanism of vitamin C transport and accumulation is by SVCT1 and SVCT2. Both SVCT1 and SVCT2 are remarkably specific for ascorbic acid [37–39]. Intravenous injection of ascorbic acid produces blood concentrations that are as much as 70-fold greater than those observed after oral doses [40], indicating that SVCT1 activity can be a limiting factor in the determination of blood ascorbic acid. Deletion of the SVCT1 gene has been shown to result in 7- to 10-fold higher urinary loss of vitamin C, with blood concentrations of vitamin C that were 50–70% lower than those of the wild-type littermates [41]. Homozygous SVCT2 knockout (slc23a2–/–) mice survive development in utero, but die within min-
utes of birth from what appears to be an impairment of the central nervous system involving a cerebral hemorrhage and failure to breathe [42]. Unlike the complete SVCT2 knockout mice, the heterozygous SVCT2 (slc23a2+/-) animals grow to adulthood, but they have low ascorbic acid levels in most tissues [42]. It is plausible that genetic variation(s) in SVCT1 or SVCT2 could affect transcription, regulation, mRNA stability, translation, post-translational processing, or membrane trafficking [22]. If any of these events occur, there could be functional consequences to the transport activity of these proteins, and serum ascorbic acid concentrations could be affected.

Functional studies in the Xenopus laevis oocyte expression system did not show significant differences in transport function between the proteins reflecting the variant genotypes of SVCT1 [43]. Additional in vitro studies examining the functional consequences of SVCT1 and SVCT2 genetic polymorphisms are needed. A kinetics trial that measures each genotype’s serum ascorbic acid response to an administered dose of vitamin C over a specified time period could provide further insights. Much is still not known about the absorption, transport and metabolism of vitamin C, and individual variability in serum ascorbic acid could also be due to a mechanism yet to be elucidated. For example, it is not yet known how ascorbic acid leaves the intestinal cells and enters the blood. SLC23A1 and SLC23A2 are the only two characterized members of the solute carrier family 23, for SLC23A3 and SLC23A4 are orphan members not yet characterized [44].

Strengths of this study include its relatively large sample size, the ability to control for multiple confounders, and the availability of detailed dietary information. Although measurement error associated with the FFQ could result in the inaccurate reporting of dietary data, estimated vitamin C intakes for men and women in our study are comparable to those reported in previous studies [45, 46], especially when supplement users are excluded. Only a single measurement of serum ascorbic acid was used, however, a study measuring the intra-individual variability of blood concentrations of ascorbic acid found that only one ascorbic acid measurement is needed to ensure that the observed correlation is within 10% of the true correlation [47]. A urine analysis of ascorbic acid metabolism end products would have been valuable to measure the vitamin C that is excreted in the urine [48] and oxidative stress. However, our study subjects are young and healthy population and, therefore, relatively free of chronic disease and major oxidative stress. The age range of the subjects is ideal for this project as sodium-dependent vitamin C transport declines with age [49, 50]. It is unknown whether replication in older populations would see a more or less pronounced genotype effect.

In summary, the findings from the present study indicate that individuals may differ in their serum ascorbic acid concentrations, regardless of dietary vitamin C, due to genetic variation in SVCT1. Our findings also demonstrate that SVCT genotypes modify the strength of the correlation between serum ascorbic acid and dietary vitamin C. The results of the present study could help to understand the role of vitamin C in chronic disease by improving the measurement of exposure by accounting for vitamin C transporter genotypes in investigations of vitamin C.

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References


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