Association between a SLC23A2 gene variation, plasma vitamin C levels, and risk of different diseases

ABSTRACT:

Background: Vitamin C is an important plasma water-soluble antioxidant that plays an essential role in the absorption of iron, detoxification of exogenous compounds, and remaking vitamin E for the protection of lipid membranes. In addition, vitamin C is essential in the synthesis of collagen. Vitamin C concentrations of plasma are determined by dietary intake and genetic factors. Ascorbic acid is the functional form of vitamin C, which is transported into the cell through sodium vitamin C transporters (SVCTs). There are two forms of SVCTs which are SVCT1 encoded by the SLC23A1 gene and SVCT2 encoded by the SLC23A2. The SLC23A2 gene locus on human chromosome 20P12. It expresses in most human tissues, except lung and skeletal muscle that it is important in regulating the intracellular concentration of ascorbic acid to protect the cell from oxidative stress and promote type 1 collagen maturation. Maintaining proper concentrations of plasma and cellular vitamin C concentration is important for the normal metabolic function of the body and preventing several diseases. In the contrast, a low concentration of vitamin C caused by SLC23A2 variation can cause several chronic diseases. Our systematic review discusses four diseases related to the variation of SLC23A2 gene and plasma vitamin C levels which are glaucoma, acute coronary syndrome among women, gastric cancer, and HPV16-associated head and neck cancer.

Method: By using NCBI databases, specifically GenBank to analyze DNA sequence and mRNA sequence of SLC23A2 gene. GenBank file format was helpful to extract an accession number of the gene, number of amino acids, number of exons and introns, and length of nucleotides. FASTA format was also useful to retrieve the nucleotide sequence and get the function of the protein. BLAST was used to compare the protein product of the SLC23A2 gene between humans and *Macaca mulatta* (Rhesus monkey).

Results: the accession number of the SLC23A2 gene was NC_000020.11, the number of exons found was 18, and the gene was located in chromosome 20. This gene encodes one of the two required transporters, and the encoded protein accounts for tissue-specific uptake of vitamin C.

This gene had an official symbol of SLC23A1. And they found a significant association between the single-nucleotide polymorphism (SNP) rs1279683 (A > G) in SLC23A2 and an increased risk of POAG in homozygous G allele (GG) carriers. Also, POAG patients with this SNP appear to have a significantly lower level of plasma vitamin C compared to other genotypes. Finally, many organisms have the same gene, such as dogs, mice, rats, and chicken**s.**

Conclusion: there is a significant association between SLC23A2 gene mutation, increased risk for vitamin C deficiency, and several diseases. SNP in the SLC23A2 gene was significantly associated with a higher risk of POAG in GG allele carriers as well as lower plasma vitamin C concentration.

Keywords: SLC23A2 gene, vitamin C, dietary, ascorbic acid, SVCT2, glaucoma, and HPV16.

INTRODUCTION:

Vitamin C is an important plasma water-soluble antioxidant that plays essential roles in the absorption of iron, detoxification of exogenous compounds, and remaking vitamin E for the protection of lipid membranes (Shaghaghi, Kloss and Eck, 2016). In addition, vitamin C is essential in the synthesis of collagen. Therefore, vitamin C deficiency may decrease the collagen content of the atherosclerotic plaques leading to vulnerable plaques being more likely to rupture (Dalgard *et al*, 2013). Vitamin C concentrations of plasma are determined by dietary intake and genetic factors. Ascorbic acid is the functional form of vitamin C, which is transported into the cell through sodium vitamin C transporters (SVCTs). There are two forms of SVCTs which are SVCT1 encoded by the SLC23A1 gene and SVCT2 encoded by the SLC23A2. The SLC23A2 gene locus on human chromosome 20P12. It expresses in most human tissues, except lung and skeletal muscle that it is important in regulating the intracellular concentration of ascorbic acid to protect the cell from oxidative stress and promote type 1 collagen maturation.

Maintaining proper concentrations of plasma and cellular vitamin C concentration is important for the normal metabolic function of the body and preventing several diseases. In contrast, low concentration of vitamin C caused by SLC23A2 variation can cause several chronic diseases such as inflammatory bowel disease, coronary heart disease, optic neuropathy, and cancer (Shaghaghi, Kloss and Eck, 2016). Our systematic review discusses four diseases related to the

variation of SLC23A2 gene and plasma vitamin C levels which are glaucoma, acute coronary syndrome among women, gastric cancer, and HPV16-associated head and neck cancer.

Initially, the association between a SLC23A2 gene variation, plasma vitamin C levels, and the risk of glaucoma -A group of diseases that damage the optic nerve and cause blindness- in a Mediterranean population. SLC23A2 is highly expressed in the eye, and gene variation is one of the factors related to the increased risk of developing primary open-angle glaucoma (POAG) (Zanon-Moreno *et al*., 2011).

Secondly, the association between two SLC23A2 gene variations and the risk of acute coronary syndrome. Vitamin C is associated with a lower risk of coronary heart disease due to its antioxidant properties; hence vitamin C deficiency increases the risk of coronary heart disease. Furthermore, SVCT2 is expressed in metabolically highly active tissue securing intracellular ascorbate accumulation against its concentration gradient in several tissues, including the aorta (Dalgård *et al*., 2013).

Thirdly, the common genetic variants within the SLC23A2 and SLC23A1 and their risk on spontaneous preterm delivery. Vitamin C is necessary for the maintenance of collagen. So, dietary vitamin C intake is specifically associated with preterm birth by premature rupture of membranes. And it is possible that common genetic variants in vitamin C transport could contribute to the risk for preterm birth-related outcomes (Erichsen *et al.*, 2005). Many women in our society are aware of the importance of collagen during pregnancy. And they take supplements in addition to fruits and vegetables to avoid any problems.

Fourthly, variation of SLC23A2 gene and vitamin C level in the plasma and the risk of gastric cancer. Vitamin C can prevent Helicobacter pylori infection, development, and reinfection. As a result, the multistep process of GC carcinogenesis involving chronic Helicobacter pylori infection can be slowed down or partially reversed in some individuals with high intakes of vitamin C. Moreover, individuals with a high intake of food rich in vitamin C have a significantly lower risk of gastric cancer. Furthermore, variants may influence cancer risk in the distal stomach; however, the association was no longer statistically significant when they

included plasma vitamin C concentration as a variable, suggesting that these variants may not be an independent susceptibility factor for GC risk (Duell *et al*.,2013).

Finally, variation of SLC23A2 gene and plasma vitamin C levels in association with HPV16. SVCT2 protein encoded by the SLC23A2 gene regulates intracellular levels of vitamin C which protects the cell from oxidative stress and promotes type I collagen maturation. Furthermore, HPV16 infection initially occurs as a result of epithelial damage, subsequent exposure, and viral invasion of the basal epidermis (Liang *et al.*, 2002; Munger *et al.,* 2004).

In this review, five articles were analyzed. Our aim is to find out the relation between SLC23A2 gene variation, plasma vitamin C levels, and risk of different diseases. The objectives are to analyze five articles discussing the same gene, obtaining the gene, and the best alignment for it. The question from this study is; what is the association between the variation of the SLC23A2 gene, plasma vitamin C, and risk of diseases?

METHOD:

Bioinformatics involves the technology that uses computers for storage, retrieval, manipulation, and distribution of all kinds of biological data. In this project, we found the association between SLC23A2 gene variation, plasma vitamin C levels, and risk of different diseases. This is accomplished by analyzing DNA and mRNA sequences. PubMed database was used to find the five articles using different keywords such as "SLC23A2", "Solute carrier family 23 members 2", "Plasma vitamin C" and "Risk of diseases". By using the GenBank database, we got the Accession number of the gene which is NC_000020.11, the number of amino acids which is 650 aa (aa stands for???, the number of exons found is 18, the number of introns is 150976, the length of nucleotide which is 157,956 nt (nt stands for??), and the nucleotide location which is (4,852,358.5,010,313).

The nucleotide sequence in FASTA format for mRNA is

```
>NM_203327.2 Homo sapiens solute carrier family 23 member 2 (SLC23A2), transcript
variant 2, mRNA
ACCCTCTTCTGGAGCAGGGCCATTCATCTTCTCCTGCCCTTGGACATCACAGCTCCAGGAACTCAGATCT
TCAGACTCAGGGTGAAGGACACCACCAGCTTTCCAGGTTCCCCAGCTTGCAGACGGCATACGCTAGGTCT
TGACTCCACTAACGGGGACTTCTCATACGGCTTTGAACTTGGACCTTGGTGCATAAGCAAATGTAACTCA
GCGAATTGTAATGGAAAGCATATGGACAGGTCTACGCCACATCACTTAGGTGCTAAGAGATGCCGTTTGC
AGGCCTCATCTCTGCTTGAGAATCGGGGGCTCCAGGCACTAGAAGAGCCGGCTGATCCTGGGCTCCTAGC
TTGAATAAGCCTTCACTTCCAGCTGCTCTCCCCAACGGCTGTGTAAACTACTCGTTTCTCTTAATGATGG
GTATTGGTAAGAATACCACATCCAAATCAATGGAGGCTGGAAGTTCAACAGAAGGCAAATACGAAGACGA
GGCAAAGCACCCAGCTTTCTTCACTCTTCCGGTGGTGATAAATGGAGGCGCCACCTCCAGCGGTGAGCAG
GACAATGAGGACACTGAGCTCATGGCGATCTACACTACGGAAAACGGCATTGCAGAAAAGAGCTCTCTCG
CTGAGACCCTGGATAGCACTGGCAGTCTGGACCCCCAGCGATCAGACATGATTTATACCATAGAAGATGT
TCCTCCCTGGTACCTGTGTATATTTCTGGGGCTACAGCACTACCTGACATGCTTCAGCGGCACGATCGCA
GTGCCCTTCCTGTTGGCCGATGCCATGTGTGTGGGGTACGACCAGTGGGCCACCAGCCAGCTCATTGGGA
```

The nucleotide sequence in FASTA format for the gene is

```
>NC_000020.11:c5010313-4852358 Homo sapiens chromosome 20, GRCh38.p13 Primary
Assembly
ACCCTCTTCTGGAGCAGGGCCATTCATCTTCTCCTGCCCTTGGACATCACAGCTCCAGGAACTCAGATCT
TCAGACTCAGGGTGAAGGACACCACCAGCTTTCCAGGTTCCCCAGCTTGCAGACGGCATACGGTGGGACT
TCTTGGCCTTTAGAATCACGTGAGCTAATTCCTGCAATAAATCCCCTCTTTCATATCCTCTTTTTTTTTT
TTTTTTTTTGAGACGGAGTCTCACTCTGTCGCCCAGGCTGGAGTGCAGTGGCGTGATCTTGGCTCACTGC
AAGCTCCGCCTCCCGGGTTCAGTCCATTCTCCTGCCTCAGCCTCCCAAGTAGCTGGGACTACAGGCGCCT
GCAACCACGCCCGGCTAATTTTTTGTAATTTTAGTAGAGACGGGGTTTCACCACGTTAGCCAGGATGGTC
TCGATCTCCTGACCTCATGATCCGCCCGCCTCGGCCTCCCAAAGTGCTGGGATTACAGGCGTGAGCCACC
GCGCCTGGCCCATATCCTTTTATATATCCCTCTATATATCCTGTTGGTTCTGTTTCTCTGGAGAACCTTG
ACTAATTCAGTTTCCAATTCTCCAGAACCCTGGGGGTTAATCCTGAGTTCTTTCCCTTCGCATTTCACCT
CTCATCAGCGGGCAGCCCCTGTTGGTTTGGTGGAACAAGTAAAGTCATTGAGTACTAACTGAGTACTTCA
GTAGTAACCGAACTGAGAACTTACTGTGTGGTAGGCACCACGTGAGGAGCTGGCATACAGAATTAAATAA
ACCAAGACCTCTGCCCTGGATGCACTGACAATTAGTGAGGGAGAGAAACAGAAAAACAACTTATTTCCAT
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The nucleotide sequence was represented from FASTA format to get the protein function and open the file of summary.

SLC23A2 gene is located in chromosome 20. The absorption of vitamin C into the body and its distribution to organs requires two sodium-dependent vitamin C transporters. This gene encodes one of the two required transporters, and the encoded protein accounts for tissue-specific uptake of vitamin C. Previously, this gene had an official symbol of SLC23A1. Many organisms have the same gene, such as dogs, mice, rats, and chickens.

There is a homology between the SLC23A2 gene in humans and other organisms. One of these organisms is *Macaca mulatta* (Rhesus monkey) with identities 100% and gaps of 0%. There are homology and differences in the protein product of the human SLC23A2 gene with other species. This is recognized by using a BLAST website.

Table 1. Official Symbol and source

Organism / Official Symbol	**Homo sapiens** / SLC23A2	***Macaca mulatta* (Rhesus monkey)** \ SLC23A2
Also Known as	NBTL1; SVCT2; YSPL2; SLC23A1	EGK_02638
Source	Homo sapiens (human)	*Macaca mulatta* (Rhesus monkey)
Accession	NG_029959	XM_028827431
DNA length	164938 bp	150108 bp
Nucleotide length	157,956 nt	123,519 nt
Gen Base Position	1.6980	1.150108

RESULTS:

Table 2. Literature review

Number of articles	**Title**	**Author**	**Year**	**Results \ finding**
1	Association between a *SLC23A2* gene variation, plasma vitamin C levels, and risk of glaucoma in a Mediterranean population.	Zanon-Moreno *et al.*	2011	*300 participants (150 POAG cases and 150 controls). * Genotype rs1279386-G/G SNP in SLC23A2 was significantly associated with a higher risk of POAG as well as lower plasma vitamin C concentration. * No association was found between polymorphisms in the SLC23A1 gene with either plasma vitamin C concentrations or POAG risk.

2	Variation in the Sodium-Dependent Vitamin C Transporter 2 Gene Is Associated with Risk of Acute Coronary Syndrome among Women.	Dalgård *et al.*	2013	* 936 cases (226 women, 710 men) and a sub-cohort of size 1,580 (748 women, 832 men) were included. * Women with the rs6139591-T/T genotype who had a low intake of dietary vitamin C had A 5.4-fold elevated risk of ACS compared with those with the CC genotype. *Women with the rs1776964-T/T genotype with a high intake of vitamin C had a 3.4-fold increased risk of ACS compared with C/C-homozygotes with low intake. *In men, they found no clear modifying effect of diet on the association between rs6139591 or rs1776964 polymorphisms and ACS. * The authors conclude that the effects of genotype may not be entirely compensated by a high dietary intake of vitamin C.

3	Genetic Variation in the Sodium-dependent Vitamin C Transporters, SLC23A1, and SLC23A2 and Risk for Preterm Delivery.	Erichsen *et al.*	2005	* 843 participants: 271 spontaneous preterm birth cases (129 African American and 142 Caucasian) and 572 controls (237 African American and 335 Caucasian). **Preterm birth and genetic variation in SLC23A2.** *In Caucasian subjects: Three SNPs associated with the risk for preterm birth: 1) A carrier of 1 or 2 minor alleles of variant rs6139591-T of the SLC23A2 gene showed a 1.7-fold and a 2.7-fold higher risk of spontaneous preterm birth, respectively. **2)** Heterozygous individuals for rs2681116-G/A in SLC23A2 showed a 1.9-fold increased risk of preterm birth. **3)** Homozygous individuals for the T allele in rs1776964 of the SLC23A2 gene showed a decreased risk of spontaneous preterm birth. *In African American subjects: Two SNPs associated with the risk for preterm birth: 1) Homozygous individuals for the minor C allele in rs2681118 of the SLC23A2 gene carried an increased risk for preterm birth. 2) Homozygous individuals for the T allele of rs6139591 of the SLC23A2 gene had a decreased risk for preterm birth. **Preterm birth and genetic variation in SLC23A1.** * Associations have been found between haplotypes in the SLC23A1 gene and spontaneous preterm delivery. *In the Caucasian population, • Individuals heterozygous for haplotype 1 (GAGCAG) had a reduced risk for spontaneous preterm birth compared with individuals homozygous for haplotype 2 (AAGTAC). *In the African American population**,** • There was no consistent pattern of association between the five common haplotypes in SLC23A1 and spontaneous preterm birth.

4	Vitamin C transporter gene (SLC23A1 and SLC23A2) polymorphisms, plasma vitamin C levels, and gastric cancer risk in the EPIC cohort.	Duell *et al.*	2013	*1613 participants (365 patients with gastric cancer and 1284 controls). **Polymorphisms and plasma vitamin C levels** *****In SLC23A2, 1) rs6053005 TT homozygotes 2) rs6133175 GG homozygotes are associated with 24 % higher plasma vitamin C concentrations. *In SLC23A1, 1) rs11950646 GG or AG genotypes are associated with a 13 % lower plasma vitamin C concentration. 2) rs33972313 GA heterozygotes are associated with a 24 % lower concentration. * Higher intakes of vitamin C from foods are statistically significantly associated with reduced gastric cancer risk. **Polymorphisms and gastric cancer risk** In the SLC23A2 gene، **1)** The genotype rs6116569-C/T **2)** Two haplotypes: • CGTC (rs6052937, rs3787456, rs6116569, rs17339746) • ATC (rs6139587, rs6053005, rs2326576) are associated with gastric cancer risk. * No association was found with variants in SLC23A1 with gastric cancer risk**.**

5	Genetic variation in the vitamin C transporter, SLC23A2, modifies the risk of HPV16-associated head and neck cancer.	Chen *et al.*	2009	* 814 participants: 319 patients with HNSCC and 495 frequency-matched controls. * HNSCC risk was >7-fold higher in those with: • a SLC23A2 wild-type GG or heterozygous GC genotype • positive HPV16 serology • high citrus consumption * HNSCC risk was significantly reduced for those with: • rs4987219-C/C homozygotes in the SLC23A2 gene • negative HPV16 serology • low citrus fruit consumption

*POAG: primary open-angle glaucoma.

* SNP: single-nucleotide polymorphism.

* ACS: Acute coronary syndrome

* HNSCC: Head and neck squamous cell carcinoma

DISCUSSION:

Vitamin C is an essential water-soluble antioxidant. Its adequate consumption may prevent the development of different diseases. Vitamin C obtained from the diet is transported across the cell membrane by sodium Vitamin C transporters (SVCTs). Two isoforms, SVCT1 (encoded by the SLC23A1 gene) and SVCT2 (encoded by the SLC23A2 gene), play central roles in the absorption and accumulation of vitamin C in many tissues. Malfunction of SVCTs leads to reduced vitamin C in tissue and causes different diseases. In this systematic review, five articles have been evaluated in order to find out the association between a SLC23A2 gene variation, plasma vitamin C level, and risk of different diseases.

The first article studies the association between a SLC23A2 gene variation, plasma vitamin C levels, and the risk of glaucoma -A group of diseases that damage the optic nerve and cause

blindness- in a Mediterranean population. In this study, they used knowledge from other studies which show that nutritional factors like vitamin C and E may play a role in the pathogenic mechanisms of glaucoma, SLC23A2 is highly expressed in the eye, and gene variation is one of the factors related to increased risk of developing primary open-angle glaucoma (POAG) (Kannan *et al.*, 2001; Delcourt *et al.*, 2010; Fernández-Martínez *et al.*, 2011). In this study, they found a significant association between the single-nucleotide polymorphism (SNP) rs1279683 (A > G) in SLC23A2 and an increased risk of POAG in homozygous G allele (GG) carriers. Also, POAG patients with this SNP appear to have a significantly lower level of plasma vitamin C compared to other genotypes. On the other hand, no association was found between polymorphisms in the SLC23A1 gene with either plasma vitamin C concentrations or POAG risk (Zanon-Moreno, *et al.*, 2011).

The second article studies the association between two SLC23A2 gene variations (rs6139591 and rs1776964) and the risk of acute coronary syndrome. In this study, they used a piece of information from another study that Vitamin C is associated with a lower risk of coronary heart disease due to its antioxidant properties; hence vitamin C deficiency increases the risk of coronary heart disease (Ford *et al.*, 2007). In this study, they found that the genotype rs6139591 in SLC23A2 was significantly associated with ACS in women. Moreover, women with rs6139591-T/T genotype who also had a low intake of dietary vitamin C had a 5-fold elevated risk of ACS compared with those with the CC genotype. Furthermore, a woman with rs1776964-T/T genotype and a high intake dietary of vitamin C was associated with a higher risk of ACS compared with the CC genotype with low dietary intake of vitamin C. On the other hand, no association was found between rs6139591 or rs1776964 polymorphisms and ACS in men. Finally, the study concludes that the effects of these genotypes may not be fully compensated by consuming more vitamin C (Dalgård *et al.*, 2013).

In the third article, the common genetic variants within the SLC23A2 and SLC23A1 and their risk on spontaneous preterm delivery on African American and Caucasian populations were discussed. In this study, they found that genetic variants within SLC23A2 and SLC23A1 genes that were associated with the risk of spontaneous preterm delivery are different for each population. Regarding the association between genetic variants within the SLC23A2 and the risk

of spontaneous preterm delivery. In the Caucasian population, they found that three individuals' SNPs in the SLC23A2 gene were associated with preterm birth. The first SNP was 1 or 2 minor alleles of variant rs6139591-T showed a 1.7-fold and a 2.7-fold higher risk of spontaneous preterm birth, respectively. The second SNP was rs2681116-G/A, which showed a 1.9-fold increased risk of preterm birth. The third SNP was the T allele in rs1776964 showed a decreased risk of spontaneous preterm birth. However, in African Americans, they found two individual SNPs associated with preterm birth. The first SNP was a minor C allele in rs2681118 showed an increased risk for preterm birth. The second SNP was T allele of rs6139591 showed a decreased risk for preterm birth. Finally, regarding the association between genetic variants within the SLC23A1 and the risk of spontaneous preterm delivery, they found a common haplotype reduces the risk of preterm delivery in the Caucasian population which was not seen in the African American population (Erichsen *et al.,* 2005).

The fourth article studies the association between vitamin C transporter genes Polymorphisms, plasma vitamin C levels, and the risk of gastric cancer (GC). In this study, they used knowledge from other studies which show that vitamin C can prevent Helicobacter pylori infection, development, and reinfection. As a result, the multistep process of GC carcinogenesis involving chronic Helicobacter pylori infection can be slowed down or partially reversed in some individuals with high intakes of vitamin C (Zhang *et al.,* 1997; Pal *et al.,* 2011). Also, from this study, they confirmed the information that individuals with a high intake of food rich in vitamin C have a significantly lower risk of gastric cancer. Also, in this study, they found that one genotype and two haplotypes in the SLC23A2 gene were associated with gastric cancer risk, and two genotypes in SLC23A2 and two genotypes in SLC23A1 were associated with plasma vitamin C concentration. Furthermore, the association between SLC23A2 (rs6116569 and the haplotypes) and GC risk, suggests that these variants may influence cancer risk in the distal stomach; however, the association was no longer statistically significant when they included plasma vitamin C concentration as a variable, suggesting that these variants may not be an independent susceptibility factor for GC risk. Moreover, they found that SLC23A2 genotypes (rs6053005, rs6133175) were associated with higher plasma vitamin concentrations. While SLC23A1 genotypes (rs33972313, rs11950646) were associated with lower plasma vitamin concentration (Duell *et al.,* 2013).

The fifth article studies the association between SLC23A2 gene variations and the risk of HPV16-associated head and neck cancer. In this study, they used pieces of information from other articles that SVCT2 protein encoded by the SLC23A2 gene regulates intracellular levels of vitamin C which protect the cell from oxidative stress and promote type I collagen maturation. Furthermore, HPV16 infection initially occurs as a result of epithelial damage, subsequent exposure, and viral invasion of the basal epidermis (Liang et al. 2002; Munger et al. 2004). Authors from this study assert that polymorphism in SLC23A2 can be correlated with a variation in the potential strength of the epithelial surface barrier resulting in a different potential viral entry. Also, they found that the risk of head and neck squamous cell carcinoma (HNSCC) was higher in those with a SLC23A2 wild-type GG or heterozygous GC genotype, positive HPV16 serology, and high citrus consumption. While, the risk of HNSCC was significantly low for those with rs4987219-C/C homozygous in the SLC23A2 gene, negative HPV16 serology, or low citrus fruit consumption (Chen AA et al., 2009).

CONCLUSION:

In short, SLC23A2 is a protein-coding gene in the human body, and it encodes SVCT2 (sodium vitamin C transporter) which is responsible for the transport of ascorbic acid (a functional form of vitamin C) into the cells. It is concluded that there is a significant association between SLC23A2 gene mutation, increased risk for vitamin C deficiency, and several diseases. SNP in the SLC23A2 gene was significantly associated with a higher risk of POAG in GG allele carriers as well as lower plasma vitamin C concentration. Moreover, some SLC23A2 gene mutations are correlated with the acute coronary syndrome in women. Also, some SLC23A2 variations are associated with spontaneous preterm birth; some of these variations increase the risk of preterm birth, while other variations decrease the risk of preterm birth. Furthermore, a High dietary intake of vitamin C is statistically correlated with a reduced risk of gastric cancer. Some genotypes of SLC23A2 were associated with the risk of gastric cancer, and other genotypes were associated with increased vitamin C concentration. Furthermore, HNSCC risk is higher in a SLC23A2 wild-type GG or heterozygous GC genotype. Moreover, the risk of HNSCC is lower in homologous CC in the SLC23A2 gene.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCES:

1. Chen A, Marsit C, Christensen B, Houseman E, McClean M, Smith J et al. Genetic variation in the vitamin C transporter, SLC23A2, modifies the risk of HPV16-associated head and neck cancer. 2009.

2. Dalgård C, Christiansen L, Vogel U, Dethlefsen C, Tjønneland A, Overvad K. Variation in the Sodium-Dependent Vitamin C Transporter 2 Gene Is Associated with Risk of Acute Coronary Syndrome among Women. PLoS ONE. 2013;8(8):e70421.

3. Delcourt C, Korobelnik J, Barberger-Gateau P, Delyfer M, Rougier M, Le Goff M et al. Nutrition and age-related eye diseases: The Alienor (Antioxydants, lipides essentiels, nutrition et maladies oculaires) study. The journal of nutrition, health & aging. 2010;14(10):854-861.

4. Duell E, Lujan-Barroso L, Llivina C, Muñoz X, Jenab M, Boutron-Ruault M et al. Vitamin C transporter gene (SLC23A1 and SLC23A2) polymorphisms, plasma vitamin C levels, and gastric cancer risk in the EPIC cohort. Genes & Nutrition. 2013;8(6):549-560.

5. Erichsen H, Engel S, Eck P, Welch R, Yeager M, Levine M et al. Genetic Variation in the Sodium-dependent Vitamin C Transporters, SLC23A1, and SLC23A2 and Risk for Preterm Delivery. American Journal of Epidemiology. 2005;163(3):245-254.

6. Fernández-Martínez L, Letteboer S, Mardin C, Weisschuh N, Gramer E, Weber B et al. Evidence for RPGRIP1 gene as risk factor for primary open angle glaucoma. European Journal of Human Genetics. 2011;19(4):445-451.

7. Ford E, Ajani U, Croft J, Critchley J, Labarthe D, Kottke T et al. Explaining the Decrease in U.S. Deaths from Coronary Disease, 1980–2000. New England Journal of Medicine. 2007;356(23):2388-2398.

8. Kannan R, Stolz A, Ji Q, Prasad P, Ganapathy V. Vitamin C Transport in Human Lens Epithelial Cells: Evidence for the Presence of SVCT2. Experimental Eye Research. 2001;73(2):159-165.

9. Liang W, Johnson D, Ma L, Jarvis S. Regulation of the human vitamin C transporters expressed in COS-1 cells by protein kinase C. American Journal of Physiology-Cell Physiology. 2002;283(6):C1696-C1704.

10. Münger K, Baldwin A, Edwards K, Hayakawa H, Nguyen C, Owens M et al. Mechanisms of Human Papillomavirus-Induced Oncogenesis. Journal of Virology. 2004;78(21):11451-11460.

1. Pal J, Sanal MG, Gopal GJ.Vitamin-C as anti-Helicobacter pylori agent: more prophylactic than curative- Critical review. *Indian J Pharmacol*,2011

11.Shaghaghi MA, Kloss O, Eck P. Genetic variation in human vitamin C transporter genes in common complex diseases. Advances in Nutrition. 2016;7(2):287–98.

12.HM Zhang, N W, O M, T Y. Vitamin C inhibits the growth of a bacterial risk factor for gastric carcinoma: Helicobacter pylori [Internet]. Cancer. U.S. National Library of Medicine; 1997 [cited 2021Dec15]. Available from: https://pubmed.ncbi.nlm.nih.gov/9366290/

13. Juan I. Young, Stephan Züchner, Gaofeng Wang Regulation of the Epigenome by Vitamin C, Annual Review of Nutrition 2015 35:1, 545-564

14. Alexander J. Michels, Tory M. Hagen, Balz Frei Human Genetic Variation Influences Vitamin C Homeostasis by Altering Vitamin C Transport and Antioxidant Enzyme Function, Annual Review of Nutrition 2013 33:1, 45-70