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Associations of Serum Vitamins with HPV Infection and CIN2+ Amonguyghur Women in Rural China

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Serum Vitamins; HPV; CIN2+; Association; Rural

1. Abstract

1.1. Background: The Uyghur is a minority with rich ethnic customs due to unique geographical environment and dietary habit. Cervical cancer incidence of Uyghur was higher than the other minority, even the HPV infection rate was low.

1.2. Objective: We assume some factors other than HPV infection or factors which may accelerate the procedure of HPV infection develop to cervical cancer may exist.

1.3. Design: A total of 833 women from Maralbexi county, Xinjiang were selected for a case-control study between March 1, 2014 and June 15, 2014. Blood specimens were collected, serum vitamin (vitamin A, C, D3 and E) assays were carried out by reverse-phase high-performance liquid chromatography (HPLC), serum vitamin B12 and folate were carried out by Enzyme-linked Immuno-absorbent Assay (ELISA). Relations between different level of serum vitamins with HPV infection and CIN2+ was analysed. Mean ± standard deviation is used for measurement data and rate is used for enumeration data. Binomial classification Logistic regression analysis is used for multivariate analysis. $P<0.05$ were considered as statistically significant.

1.4. Results: Serum vitamin D higher than 49.6434ng/L was the risk factor, while serum level of folate higher than 17.6705 ug/L was the protective factor of HPV infection for Uyghur women. Serum level of vitamin C higher than 0.6857ug/L was the protective factor for CIN2+, and no risk factor of serum vitamin was found for CIN2+($P<0.001$).

1.5. Conclusions: Our data confirm the importance of antioxidant vitamins in the process of carcinogenesis of CIN2+ among Uyghur ethnics. The implication in terms of prevention is to encourage intake of appropriate fresh vegetables and fruits rich in antioxidant vitamins. Replication of this study in different populations may give further credence to its findings.

2. Introduction

Cervical cancer was the third most common cancer in women worldwide, and the fourth most prevalent type of malignancy (62,000 new cases and 30,000 deaths) in China [1]. Although the prevalence is moderate compared with other regions, the mortality rate remains high especially in rural areas [2].

The occurrence and development of cervical cancer is a long and slow process, also is the result of long-term interaction between body's internal and external environment. In normal circumstances, the body contains a variety of vitamin which would keep in a state of balance. If the balance was break, various diseases would occur. During recent decades, antioxidant vitamins have received much attention in relation to cancer prevention, particularly because they may prevent free-radical damage to DNA by neutralizing free radicals and oxidants, enhance the immune system and inhibit insulin-like growth factor (IGF) [3, 4]. Recent years, a meta-analysis of case-control studies documented an inverse association between increased intake of antioxidant vitamins (such as β-carotene, vitamin E, and vitamin C) and risk of cervical cancer [5].

The Uyghurs is a minority with rich ethnic customs due to unique geographical environmental backgrounds. Reports show that, Uyghur minority in south Xinjiang prefer meet instead of vegetables and fruits. 88.5% urban citizen would eat meat product every day, and intake eggs, fresh vegetables and fruits once a week, only 30% citizen occasionally uptake beans. The special dietary habit will cause the lack of vitamins and micronutrients to a certain extent [6]. Cervical cancer incidence of Uyghurs from Xinjiang Uyghur Autonomous Region was 527/100,000 [7], much higher than the national average of 126.94/100,000 [8]. Morbidity and mortality of cervical cancer in Uyghur minority ranked the highest among minorities nationwide, even higher than the ethnicities from same area [9]. Human Papillomavirus, which is considered to be the major risk factor of cervical cancer, were found in low infection rate in Uyghur healthy population by our former study. This is not accordance with the current epidemiological status of Uyghur cervical cancer [10].We assume some factors other than HPV infection or factors which may accelerate the procedure of HPV infection develop to cervical cancer may exist. To examine whether the body's internal environmental factors will influence Uyghur women's human papillomavirus infection status and cervical lesions occurrence, we conducted a case-control study to evaluate the association of serum vitamins with HPV and CIN2+ in Uyghur women, Xinjiang China in this study.

3. Methods

3.1. Study Design and Participants

5045 women were recruited to a cervical cancer screening survey in Maralbexicounty, Xinjiang between March 1, 2014 and June 15, 2014. Care HPV, LBC (Liquid Based Cytology), VIA and VILI test were adopted to screen for cervical cancer, and cervical biopsy under the colposcopy was performed to the women with any of the positive results. 646 women who accepted colposcopy and cervical biopsy were randomly selected to the current study. Blood specimens were obtained from participants for vitamin test before the colposcopy. Meanwhile, 187 patients in Xinjiang Medical University Affiliated Tumor Hospital, who was tested by care HPV, and came from Maralbexi county were also brought into the survey. Ultimately, a total of 833 rural Uyghur women were recruited to this study. Inclusion criteria were age between 20-65 years old, had sexual life, no cervical lesion or tumor history, never undergone chemotherapy or radiotherapy, never used drugs or supplementations contain vitamins. Written informed consent was obtained from every participant before the study. This research is not a clinical trial and therefore does not need to be registered.

Two case groups were designed for the study, one included women with HPV positive without considering other consequences(n=551), another group selected women who were pathologically diagnosed as cervical intraepithelial neoplasia(CIN) 2 and higher level lesions, also invasive cervical cancers (n=150). Control groups were include HPV negative for group 1 (n=332) and normal or CIN1 of pathological diagnosis for group 2(n=683). We obtained written consent from each study participant before collecting blood, secretion or tissue samples, and the Ethnics Committee of the Affiliated Tumor Hospital of Xinjiang Medical University approved the study protocol. The methods were carried out in accordance with the approved guidelines (Figure 1).

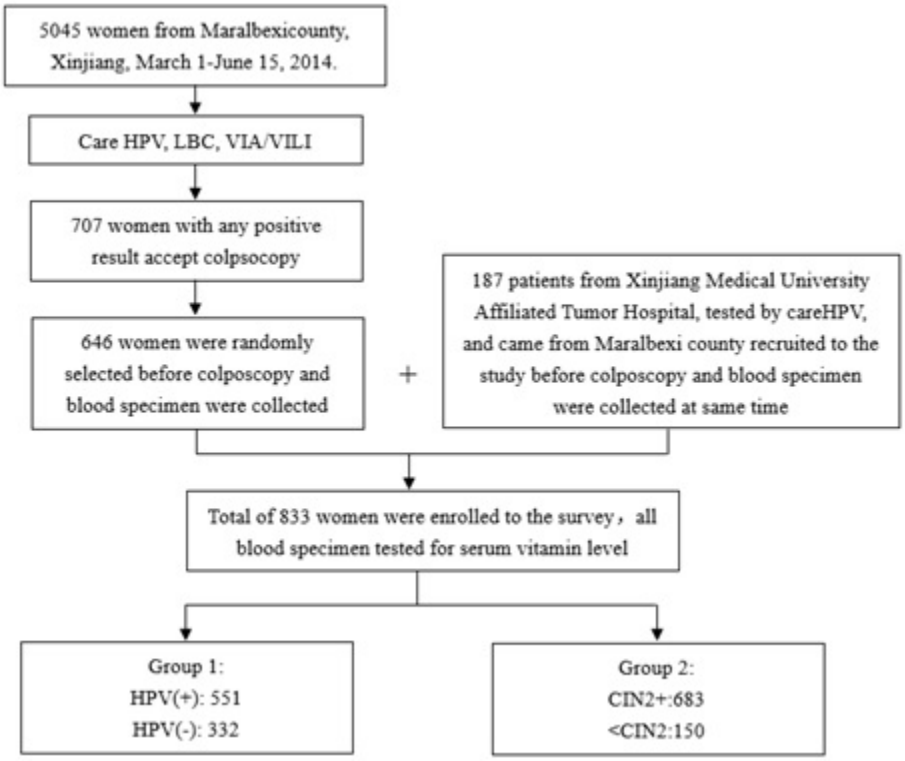

Figure 1

3.2. Measurement of serum vitamin A, C, D3 and E concentrations

Blood samples were collected from 833 participants, serum free specimens were obtained within 2 hours and storing at −80℃ before the detection. Serum vitamin A, C, D3 and E were tested by reverse-phase high-performance liquid chromatography (HPLC) according to the method developed by Burriet al [11] with little modifications. In brief, (1) extract serum samples for vitamin A, D3 and E: 400μlwere mixed with 400μl 95% aqueous ethanol as the internal standard, vortex oscillation for 15 min, and then mixed with an equal volume of n-hexane. Then vortex shocked and centrifuged miscible liquids, took the supernatant. The supernatant was dried under a stream of nitrogen and dissolved in 400μl methanol, and then collected the filtrate that was filtered with 0.22 microns of microporous membrane filter.(2)extract serum samples for vitamin C: 100 μl of serum samples were mixed with 250μlperchlorate - oxalic acid -tetraacetic acid disodium - dithiothreitoland 10μl water as the internal standard, vortex oscillation for 3 min, then centrifuged miscible liquids, took the supernatant and filtered with 0.22 microns of microporous membrane filter. Finally, the filtrate was collected and analyzed using a VP-OD Schroma to graphic analytical column (Agilent, 4.6mm×250mm). Peaks were detected at a wavelength of 325 nm for vitamin A, 243 nm for vitamin C, 265 nm for vitamin D3 and 292 nm for vitamin E by a Waters 2998 diode-array detector (Waters, USA).

3.3. Measurement of serum vitamin B12 and folate concentrations

Serum vitamin B12 and folate were detected by Enzyme-linked Immuno-absorbent Assay (ELISA) according to previously described methods [12]. 100μl of serum specimen and 100μl of sample diluent were respectively added into hole of enzyme label plate and hatched in 37℃. Discarding liquid and washing each hole of enzyme label plate with washing buffer and injecting biotin antibody working liquid, ABC working liquid and TMB chromogenic working liquid in turn. When standard samples had obvious gradient blue, we injected TMB terminated liquid into hole of enzyme label plate to terminate reaction. Finally, we measured OD value at a wavelength of 450 nm using automatic enzyme standard instrument, and then according to the OD value and the concentration of the reference substance, we got standard curve of vitamin B12 and folate.

3.4. Statistical Analysis

All analyses were performed using SPSS version 19.0 (SPSS Inc, USA).Mean± standard deviation is used for measurement data and rate is used for enumeration data. Using dummy variables deal with disorderly classification variables and orderly classification variables. Non-normal distribution of measurement data was used the median and interquartile range to analyze the statistical significance. Chi-square test is used for univariate analysis and factors that $P < 0.1$ were incorporated into multiple factors analysis. Binomial classification Logistic regression analysis is used for multivariate analysis. $P<0.05$ were considered as statistically significant.

4. Results

4.1. Association of serum Vitamins and HPV infection of Uyghur women

A total of 833 participants were brought into the analyses, in which551 participants were HPV positive and 282 participants were HPV negative. The serum level of vitamin C, A, D3, E, B12 and folate were 0.03376ug/L (0.0289ug/L), 1.7948umol/L (0.8342umol/L), 42.5473ng/L (25.8258ng/L), 284.8363nmol/L (190.6264 nmol/L), 78.6058ng/L (27.0649 ng/L) and 12.8469ug/L (7.9812ug/L), respectively in HPV positive group, and were 0.03695ug/L (0.0324ug/L), 1.9678umol/L (0.7926umol/L), 38.5958ng/L (24.6447ng/L), 289.7459nmol/L (192.63348nmol/L), 76.2376ng/L (25.6152ng/L) and 14.4683ug/L (7.5360ug/L), respectively in HPV negative group.

The level of all participants' serum vitamins were divided into four ranks(Q1-Q4) according to the interquartile range of HPV(-) group, in order to increase the accuracy of the calculation. The univariate analysis showed the serum level of vitamin A, D3, B12 and folate were statistically different between HPV(+) and HPV(-), but no statistically significance was found for vitamin C and E (Table 1).

The level of serum vitamin A, vitamin D3, vitamin B12 and folate were brought into Logistic regression model for multivariate analysis based on the results of univariate analysis. Entry criteria = 0.05 and exclusion criteria= 0.10.As it shown in Table 2, the results of multivariate analysis indicated that the level of serum vitamin D higher than 49.6434ng/L was the risk factor of HPV infection for Uyghur women, while serum level of folate higher than 17.6705 ug/L was the protective factor of HPV infection for Uyghur women in Maralbexi county, Kashgar.

Table 1: Univariate analysis ofSerum Level of vitamins and HPV infection in Uyghur Women

Serum Vitamins	HPV infection（N/%）		χ^2	*P*
	Negative(282/33.85）	Positive(551/66.15）		
Vitamin C (ug/L)			4.407	0.221
Q1 (0.0025～)	70/24.82	142/25.77		
Q2 (0.0248～)	71/25.18	172/31.22		
Q3 (0.0371～)	70/24.82	117/21.23		
Q4 (0.0571～)	71/25.18	120/21.78		
Vitamin A (umol/L)			17.14	0.001
Q1 (1.0057～)	70/24.82	158/28.68		
Q2 (1.5158～)	71/25.18	152/27.59		
Q3 (1.9683～)	70/24.82	74/13.43		
Q4 (2.3081～)	71/25.18	167/30.31		
Vitamin D_{3} (ng/L)			19.45	< 0.001
Q1 (18.1347～)	70/24.82	71/12.89		
Q2 (25.3042～)	71/25.18	155/28.13		
Q3 (38.6680～)	70/24.82	150/27.22		
Q4 (49.6434～)	71/25.18	175/31.76		
Vitamin E (nmol/L)			0.594	0.898
Q1 (114.2463～)	26/24.5	134/24.32		
Q2 (185.8268～)	27/25.5	152/27.59		
Q3 (290.5572～)	27/25.5	134/24.32		
Q4 (379.1603～)	26/24.5	131/23.77		
Vitamin B_{12} (ng/L)			9.663	0.022
Q1 (22.1506～)	70/24.82	152/27.59		
Q2 (52.0990～)	71/25.18	96/17.42		
Q3 (76.5989～)	70/24.82	125/22.69		
Q4 (98.3387～)	71/25.18	178/32.30		
Folate (ug/L)			11.24	0.011
Q1 (6.1187～)	70/24.82	160/29.04		
Q2 (10.5653～)	71/25.18	172/31.22		
Q3 (14.7200～)	70/24.82	129/23.41		
Q4 (17.6705～)	71/25.18	90/16.33		

Table 2: Multivariate Analysis of Serum vitamins and HPV infection in Uyghur Women

Serum Vitamins	Regression Coefficient	Standard Error	Wald chi-square	*OR*	95% CI	*P*
Vitamin D_{3} (ng/L)			11.643			＜0.001
Q2 (25.3042～)	0.296	0.238	3.485	1.984	0.910-4.328	0.082
Q3 (38.6680～)	0.301	0.259	3.924	2.735	0.931-6.076	0.073
Q4 (49.6434～)	0.384	0.277	7.652	2.468	1.133-5.378	0.018
Folate (ug/L)			8.449			0.007
Q2 (10.5653～)	-0.187	0.122	0.094	0.989	0.494-1.981	0.952
Q3 (14.7200～)	-0.229	0.145	1.326	0.632	0.306-1.303	0.191
Q4 (17.6705～)	-0.348	0.236	5.573	0.462	0.217-0.982	0.034

4.2. Association of serum Vitamins and CIN2+ of Uyghur women

According to the pathology results, 150 participants were diagnosed as high level cervical lesions (CIN2 or higher)), while-583women were diagnosed as normal or CIN1.The level of serum vitamin C, A, D3, E, B12 and folate were 0.5592ug/L (0.2603ug/L), 1.7253umol/L (0.7958umol/L), 41.5930ng/L (22.8541ng/L), 284.8674nmol/L (186.1477nmol/L), 77.4902ng/L (53.922ng/L) and 14.0860ug/L (6.81ug/L), respectively in the control group(≤CIN1); and the serum level of vitamin C A, D3, E, B12 and folate were 0.4672ug/L(0.6583ug/L), 1.7948umol/L (0.8342umol/L), 37.6481ng/L(27.7358ng/L), 282.7460nmol/L(191.0267nmol/L), 74.7268ng/L(55.0875ng/L) and 11.9846ug/L(5.7528ug/L), respectively incase group(≥CIN2).

Participants' serum vitamins were divided into four ranks(Q1-Q4) based on the interquartile range of control group. The univariate analysis indicated that the level of serum vitamin C, A and D3 were different between case group(χ2=29.528, 12.759, 8.833 ， P=0.000, 0.005, 0.032)and control group. But there were no statistically difference for vitamin E, B12 and folate (Table 3).

Multivariate analysis between vitamins and high-grade cervical intraepithelial neoplasia and cancer were shown in Table 4. According to the results of univariate analysis, the serum level of vitamin C, A, D3 and B12 were brought into Logistic regression model for multivariate analysis. The multivariate analysis indicated that the serum level of vitamin C higher than 0.6857ug/L was the protective factor for CIN2+ of Uyghur women in Maralbexi county, Kashgar. No risk factor of serum vitamin was found for CIN2+.

Table 3: Univariate analysis ofSerum Level of vitamins and CIN2+ in Uyghur Women

Serum Vitamins	Cervical Lesions (N/%)		χ^2	*P*
	≤CIN1（683/81.99）	≥CIN2（150/18.01）		
Vitamin C (ug/L)			29.528	< 0.001
Q1 (0.1397～)	170/24.89	60/40.0		
Q2 (0.4254～)	171/25.04	40/26.67		
Q3 (0.5592～)	171/25.04	40/26.67		
Q4 (0.6857～)	171/25.04	10/6.67		
Vitamin A (umol/L)			12.759	0.005
Q1 (1.0057～)	170/24.89	58/38.67		
Q2 (1.5202～)	171/25.04	28/18.67		
Q3 (1.9294～)	171/25.04	28/18.67		
Q4 (2.3677～)	171/25.04	36/24.00		
Vitamin D3 (ng/L)			8.833	0.032
Q1 (18.1347～)	170/24.89	46/30.67		
Q2 (29.6828～)	171/25.04	48/32.00		
Q3 (41.5930～)	171/25.04	32/21.33		
Q4 (52.5369～)	171/25.04	24/16.00		
Vitamin E (nmol/L)			2.426	0.489
Q1 (114.2463～)	170/24.89	46/30.67		
Q2 (190.2141～)	171/25.04	32/21.33		
Q3 (284.8674～)	171/25.04	35/23.33		
Q4 (376.3618～)	171/25.04	37/24.67		
Vitamin B12 (ng/L)			5.424	0.143
Q1 (22.1506～)	170/24.89	37/24.67		
Q2 (49.6857～)	171/25.04	25/16.67		
Q3 (77.4902～)	171/25.04	44/29.33		
Q4 (103.6077～)	171/25.04	44/29.33		
Folate (ug/L)			5.493	0.139
Q1 (6.1187～)	170/24.89	44/29.33		
Q2 (10.3647～)	171/25.04	44/29.33		
Q3 (14.0860～)	171/25.04	37/24.67		
Q4 (17.1837～)	171/25.04	25/16.67		

Table 4: Multivariate Analysis of Serum vitamins and CIN2+ in Uyghur Women

Serum Vitamins	Regression Coefficient	Standard Error	Wald chi-square	*OR*	95% CI	*P*
VC (ug/L)			13.585			< 0.001
Q2 (0.4254～)	-0.276	0.224	1.384	0.775	0.365-1.643	0.271
Q3 (0.5592～)	-0.325	0.254	1.497	0.686	0.322-1.461	0.246
Q4 (0.6857～)	-0.426	0.337	10.165	0.217	0.074-0.635	0.008

5. Discussion

According to reports, a variety of antioxidant vitamins, such as vitamin A and C could reduce the risk of CIN and HPV virus load. Lack of vitamin A, C, E, folate and B carotene might increase the risk of cervical cancer. The biological mechanisms might explain the important role of antioxidant vitamins in preventing the development of cervical carcinogenesis. Antioxidant vitamins, such as α -carotene, β -carotene, vitamin E, and vitamin C could act as efficient scavengers of free radicals and oxidants to prevent free-radical damage to DNA(13). Moreover, if the free radicals and oxidants were not neutralized by antioxidant molecules, inflammatory processes could lead to extensive damage to DNA proteins [14]. It has also been hypothesized that possessing antioxidant properties may protect the immune system from oxidative damage, enhance immune responsiveness, and inhibit IGF because immune cells are particularly vulnerable to oxidative stress [3,4]. In addition, animal experiments have suggested that supplementing vitamins A, C, and E prevents the development of pre-neoplastic lesions in rats [15]. Thus, antioxidant status in vivo may protect cellular function from damage.

Researches reported [16-18] that vitamin C can significantly inhibit the growth of malignant tumor such as prostate cancer, liver cancer, leukemia and bladder cancer, and independently induce apoptosis of cancer cells; for tumor cells of cervical cancer patients, vitamin C can not only inhibit the DNA synthesis and cell proliferation, but also reduce the peroxidase and increase production and aggregation of hydrogen peroxide. As an electron donor, vitamin C has oxidation resistance in the human body. A large number of epidemiological studies found that the people who meal food rich in vitamin C had lower incidence of the tumor. The anti-cancer mechanism of vitamin C may include:

1. Protecting DNA from damage by eliminating oxygen free radicals in the body; Bagchi [19] found that the function of vitamin C protecting DNA from damage may related to expression protein of the Bcl-2 and p53.

2. Leading to abnormal cell cycle and accelerating phosphate adenosine synthesis. Domestic study found the high levels of vitamin C could induce apoptosis of Hela, and through accelerating cyclic guanosine phosphate synthesis to inhibit tumor cell proliferation. Research results of Roomi(20)etc showed that vitamin C could enhance the inhibitory effect of other drugs for the growth of Hela.

3. Preventing synthesis of hyaluronidase and nitrosamines. They associate with occurrence and development of tumor, compete with amine in combination with nitrates, vitamin C can inhibit the formation of hyaluronidase. The results of our study showed that the higher level of serum vitamin C is the protective factor of cervical intraepithelial neoplasia and cervical cancer of Uyghur women in Marabexicounty.

Being a carbon unit, folate participatesin the process of nucleic acid metabolism, and plays a very important role in the host defense, cell differentiation and growth and DNA repair. Studies showed that there was a close correlation between the lack of folate and tumor [21, 22]. In carcinoma tissues, such as cervical cancer, liver cancer, breast cancer,wide range of low methylation and regional high methylation of DNAoften coexistence. Folate, as a methyl donor, had a close relationship with wide range of low methylation in tumor tissue. Research results of Shikanv [23] showed that folate supplementation can significantly improve the cervical intraepithelial neoplasia and reduce the degree of lesions. Piyathilake [24] found thatpeople whohave HPV infection with low levels of serum folate are more likely to suffer from cervical cancer. Consistent with our study,the level of serum folate≥17.6705 ug/L was the protective factor of HPV infection of Uyghur women.

Vitamin D is one of the essential vitamins, its main active metabolites in the body is 1, 25-dihydroxy cholecalciferol (1, 25-(OH) 2D3).It plays an important role in regulating kidney, intestinal calcium and phosphorus metabolism and tissue differentiation.In recent years, the studies found that vitamin D could not only induce tumor cell apoptosis, promote the differentiation of tumor, but also have an important role in immune regulation(25-26).Domestic studies found that vitamin D in the tissue of chronic cervicitis, CIN and cervical cancer expression increased with the degree of pathological changes aggravated; while others showed that levels of serum 1, 25 - (OH) 2 D3 had no significant correlation with cervical cancer. Our study showed that the level of serum vitamin D3≥49.6434ng/L is the risk factor of HPV infection of Uyghur women, but had no significant correlation with the high-grade cervical intraepithelial neoplasia and cancer.

The result was other vitamins include vitamin A, E, B12 were not associated with Uyghur women'sHPV infection or CIN2+ status. Nevertheless, protective role of these vitamins in HPVinfection or cervical cancer were indicatedin relevant literatures. Rebecca L [27] had tested the hypothesis that higher dietary levels of vitamin A (retinol) or circulating levels of retinol reduce the risk of HPV persistence by a prospective cohort study, and findings of French AL [26] suggests that retinol deficiency may contribute to the development of cervical SILs in HIV-infected women.The study refer to vitamin E found the adjusted mean concentrations of serum alpha- and gamma-tocopherol, which were the main components of vitamin E, were lower among women with HPV positive compared with HPV negative, Independent of HPV status, alpha-tocopherol was significantly inversely associated with grade of cervical dysplasia [28]. A reportindicated that methyl donor micronutrients, folate and vitamin B12, may play an important role in maintaining a desirably high degree of methylation at specific CpG sites in the HPV E6 promoter and enhancer that are associated with the likelihood of being diagnosed with CIN 2+ [29]. Different results may be explained by limited sample size, regional variation in antioxidant vitamins contained in foods.

This study provided evidence for a protective role of the serum concentration of antioxidant vitamins (vitamin C and folate) in the etiology of HPV infection and cervical lesionsof Uyghur women, while the vitamin D3 played the risky role in HPV infection. Our data confirm the importance of antioxidant vitamins in the process of carcinogenesis. The implication in terms of prevention is to encourage intake of appropriate fresh vegetables and fruits rich in antioxidant vitamins. The limitation of current study was the size and source of sample, replication of this study in different populations with large sample size may give further credence to its findings.

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