

# Associations between Antioxidants and High-risk HPV Infection in women

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## Background

HPV infection is a major risk factor for cervical cancer and precancerous lesions. Oxidative stress, (reflected by some antioxidant markers), may act as a co-factor. However, the association between antioxidants and oncogenic or high-risk HPV infection remains unclear.

## Objectives

Identify antioxidants associated with vaginal HR-HPV infection in women.

Table 1. demographic data

Variable	Total (wt%) <sup>1</sup>	Vaginal HPV, wt% <sup>1</sup>			p-value <sup>2</sup>
		No	Low-risk	High-risk	
Total	11070 (100)	59.7	21.2	19.1	-
Age					
18-26	2510 (17.6)	50.6	18.4	31.1	<0.001
27-35	2343 (20.8)	57.8	20.6	21.7	
36-45	2845 (27.2)	60.3	23.2	16.5	
46-59	3372 (34.5)	64.9	21.5	13.6	
Race					
Non-Hispanic White	4180 (63.3)	63.2	19.2	17.6	<0.001
Non-Hispanic Black	2589 (13.5)	41.1	32.0	26.9	
Mexican American & other Hispanic	3241 (15.9)	57.6	22.6	19.8	
Others	1060 (7.2)	67.2	16.3	16.6	
Education					
<high school	791 (4.3)	59.1	22.4	18.5	<0.001
high school	3611 (31.3)	53.0	24.4	22.7	
>high school	5793 (64.4)	63.2	19.8	17.0	
Marital status					
Married/live with partner	6273 (64.0)	67.6	18.5	13.9	<0.001
Never married	2593 (19.5)	48.4	20.8	30.8	
Widowed/Divorced/Separated	1830 (16.5)	42.8	32.3	24.9	
Poverty index ratio					
≤1	2689 (17.2)	47.0	24.9	28.2	<0.001
1.1-2	2529 (19.5)	53.4	25.3	21.3	
2.1-4	2550 (28.0)	62.6	19.4	18.0	
4.1-6	2550 (28.0)	62.6	19.4	18.0	
>4	2530 (35.3)	67.8	18.2	14.0	
Obesity status (Body Mass Index)					
Underweight or normal (<25)	4179 (41.6)	59.8	19.5	20.7	0.005
Overweight (25-29.9)	2774 (26.3)	60.3	21.7	18.0	
Obese (≥30)	3671 (32.2)	59.3	22.9	17.9	
Smoking					
Never	6703 (61.5)	65.0	18.2	16.7	<0.001
Former	1487 (16.9)	61.7	22.6	15.7	
Current	2147 (21.6)	43.5	29.1	27.4	
Number of days use alcohol past year					
0	3366 (30.3)	67.5	18.5	14.0	<0.001
1-25	3035 (35.8)	58.8	21.7	19.5	
>25	2417 (33.9)	55.4	22.5	22.2	
Lifetime illegal substance use					
No	5327 (51.4)	66.2	18.2	15.6	<0.001
Yes	4034 (48.6)	53.3	24.7	22.0	
Number of sex partners past year					
0	1546 (15.9)	65.7	21.5	12.8	<0.001
1	6422 (72.7)	63.5	20.1	16.4	
≥2	1144 (11.5)	27.5	29.7	42.9	

<sup>1</sup>wt%: weighted % based on the NHANES sampling weights

<sup>2</sup>Tested using the Rao-Scott chi-square test

## Method

- Nutritional antioxidant data:** the average of the two 24-hour dietary intake results, log transformed
- Study population:** HPV infections evaluated by the 14-year (2003-2016) National Health and Nutrition Examination Survey (NHANES) for 11,070 women aged 18-59 years.
- Classification of HPV infections:** Defined as High risk if any HR type tested positive; low risk if no high-risk type positive but any low-risk type positive  
**Low risk:** 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, 89, IS39  
**High risk:** 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
- Statistical Analysis:**  
 For demographic data - weighted descriptive statistics  
 For evaluation of demographic data and HPV types (adjusted covariates selection) - Rao-Scott Chi-square  
 For relationship between antioxidants and HPV types - univariate/multivariate multiple logistic regression model

Table 2. Antioxidant VS. HPV status

Biomarker (unit)	Unadjusted		Adjusted <sup>1</sup>		Sample Size
	Low-risk HPV Vs. No HPV OR (95% CI)	High-risk HPV Vs. No HPV OR (95% CI)	Low-risk HPV Vs. No HPV OR (95% CI)	High-risk HPV Vs. No HPV OR (95% CI)	
<b>Endogenous antioxidants</b>					
Albumin (g/L)	0.25(0.13,0.49)***	0.16(0.07,0.34)***	0.68(0.29,1.63)	0.29(0.11,0.76)*	7405
<b>Nutritional antioxidants</b>					
Vitamin A (mcg)	0.84(0.76,0.93)**	0.75(0.68,0.82)***	0.94(0.84,1.05)	0.89(0.8,0.98)*	7548
Vitamin B2 (mg)	0.77(0.67,0.89)**	0.72(0.63,0.83)***	0.88(0.75,1.04)	0.84(0.72,0.98)*	7548
Vitamin E (mg)	0.77(0.68,0.86)***	0.7(0.62,0.79)***	0.84(0.70,1.00)*	0.83(0.7,0.97)*	7548
Folate (mcg)	0.73(0.64,0.84)***	0.72(0.63,0.82)***	0.81(0.69,0.95)**	0.79(0.69,0.92)**	7548

\*: p<0.05, \*\*:p<0.01; \*\*\*:p<0.001 based on multinomial logistic models, bold: adjusted p<0.05 for high-risk HPV

<sup>1</sup> multinomial logistic model adjusted for 9 factors (age, race, education, income, marital status, smoking status, lifetime illegal substance use, past 12-month alcohol intake, number of sexual partners in past 12-month).

Table 3. Albumin and NAS VS. HPV status

Biomarker (unit)	Sample size	Model 1 (n=10073) <sup>1</sup>		Model 2 (n=7253) <sup>2</sup>	
		Low-risk HPV Vs. No HPV OR (95% CI)	High-risk HPV Vs. No HPV OR (95% CI)	Low-risk HPV Vs. No HPV OR (95% CI)	High-risk HPV Vs. No HPV OR (95% CI)
Albumin (g/L)					
≤39	2687	1	1	1	1
39.1-41	2349	0.91 (0.75-1.11)	0.78 (0.64-0.95)*	0.98 (0.76-1.25)	0.83 (0.65-1.06)
41.1-44	3506	0.78 (0.66-0.93)**	0.72 (0.61-0.86)***	0.92 (0.75-1.11)	0.76 (0.61-0.93)**
>44	1991	0.75 (0.62-0.92)**	0.62 (0.50-0.76)***	1.00 (0.78-1.30)	0.71 (0.54-0.93)*
<b>Nutritional antioxidant score (NAS)</b>					
Low (≤25%)	2936	1	1	1	1
Median low (25.1-50%)	2720	0.80 (0.67-0.95)*	0.73 (0.61-0.87)***	0.85 (0.69-1.05)	0.87 (0.67-1.13)
Median high (50.1-75%)	2559	0.64 (0.52-0.78)***	0.62 (0.51-0.75)***	0.79 (0.63-1.00)	0.85 (0.67-1.08)
High (>75%)	2328	0.59 (0.49-0.71)***	0.57 (0.47-0.69)***	0.69 (0.55-0.88)**	0.76 (0.59-0.97)*

## Results

- Identified serum albumin, vitamin-A, -B2, -E, and folate were inversely associated with HR-HPV infection.
- Developed the nutritional antioxidant score (NAS).
- Women with a high albumin level (Odds ratio [OR]=0.76 and 0.71 for 41.1-44 and >44 vs. ≤39 g/L) and a high NAS in the top quartile (OR=0.76 vs. the low NAS quartile group) had a lower risk of HR-HPV.

## Conclusion

- Our findings demonstrated inverse associations between the five antioxidants. The higher serum albumin and higher intake of nutritional antioxidants included vitamins A, B2, and E, and folate were associated with lower risk of HR-HPV infection. Antioxidants may provide a protective effect on HR-HPV infection, which could decrease the risk of cervical cancer development..

## Discussions

- This study cannot identify or infer a causal relationship between antioxidants and HR-HPV infection due to the usage of cross-sectional NHANES data.
- This study cannot evaluate antioxidants associated with persistent HPV infection because only one-time HPV infection was measured. Further, large and prospective study research is needed to evaluate the effect of antioxidants and persistent HR-HPV infection.
- There may be a recall bias for the self-reported health behaviors such as sex partners and alcohol intake during interview.