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Factores asociados a la infección por el virus del papiloma humano (VPH) en mujeres del noroeste de México

Associated factors with human papillomavirus (HPV) infection in adult women from northwest Mexico

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RESUMEN

Investigaciones sobre la asociación entre factores de riesgo y la infección por VPH en mujeres adultas hermosillenses no existen, y por ello se diseñó un estudio de casos y controles (1: 2) pareado por edad para analizar este problema de salud pública a nivel local. Participaron 33 y 66 mujeres con y sin VPH respectivamente (edad media = 41,8 ± 7,9 años). La diferencia de características entre grupos se probó con regresión logística condicional (univariada). La ingesta de antioxidantes se ajustó por energía total utilizando el método residual. Se generaron dos modelos de regresión logística multivariada para identificar los factores asociados con VPH. En ambos modelos, el mayor consumo de licopeno (OR = 0,96, IC =0,95- 0,99, p = 0,019) y la mayor Capacidad Antioxidante Total plasmática (CATp) (OR = 0,05, IC 95% = 0,03-0,7, p = 0,024), ajustados aún con el número de embarazos, número de parejas sexuales, y total de parejas sexuales por año, redujeron el riesgo a VPH. Los embarazos múltiples y la conducta sexual incrementaron el riesgo a VPH, y los mayores consumos de licopeno y CATp la redujeron en las mujeres de este estudio. Debe fortalecerse la educación sexual, así como el consumo de antioxidantes en las mujeres hermosillenses para prevenir el desarrollo del cáncer de cuello uterino.

Palabras clave: VPH, Antioxidantes dietarios, Capacidad antioxidante total, Noroeste de México.

ABSTRACT

Research on the association between risk factors and HPV infection in adult women from Hermosillo does not exist, so a study of cases and controls (1: 2) matched by age was designed to analyze this public health problem at a local level. Participants were 33 and 66 women with and without HPV, respectively (mean age = 41.8 ± 7.9 years). The difference in characteristics between groups was tested with conditional logistic regression (univariate). Antioxidant intake was adjusted by total energy using the residual method. Two multivariate logistic regression models were generated to identify factors associated with HPV. In both models, the higher consumption of lycopene (OR = 0.96, CI =0.95-0.99, p = 0.019) and the higher Plasma Total Antioxidant Capacity (TACp) (OR = 0.05, CI 95 % = 0.03 - 0.7, p = 0.024), even adjusted by the number of pregnancies, number of sexual partners, and total number of sexual partners per year, reduced the risk of HPV. Multiple pregnancies and sexual behavior increased the risk of HPV, whilst higher consumption of lycopene and TACp reduced it in the women in this study. Sex education should be strengthened, as well as the consumption of antioxidants in women from Hermosillo to prevent the development of cervical cancer.

Key words: HPV, Antioxidant Dietary, Total Antioxidant Capacity, Northwest Mexico.

INTRODUCTION

Cervical cancer is the most common cancer in women, with around 604 000 new cases and 342 000 deaths; with about 90% of the new cases and deaths occurring in poor countries worldwide in 2020 (WHO). Human Papilloma Virus (HPV) infection is an important factor –but not sufficient by itself– in the development of cervical cancer, and remains a serious public health problem (McMullin, 2009). In addition, age at which sexual intercourse begins, the number of partners/sexual partners, lack of condoms use, low socioeconomic status, multiparity, smoking, and low antioxidant consumption, are all also recognized risk factors for HPV infection (Liang *et al.*, 2018). Georgescu *et al.* (2018) published that a deficiency of body antioxidant compounds may result in DNA damage and low immune-competence that may promote the HPV infection and carcinogenesis. Barchitta *et al.* (2020) found that 84 HPV-positive women reported lower intake of antioxidants (zinc, manganese, and vitamins A and C) than non-infected women. Jordá *et al.* (2020) studied 505 women between 15 and 49 years old and reported higher HPV infections in both women aged 15 - 24 years and women with more sexual partners. Studies in different regions have stated that the highest prevalence of HPV is often found in women younger than 25 years of age because of their risky sexual behavior, little awareness about the HPV infection, and low rate of vaccination (Herrera-Ortiz *et al.*, 2018). In Mexico, the HPV prevalence in women ranged from 4.1 % to 65.0 % in 2016 (Bruni *et al.*, 2021); and it has been estimated that 95 % to 99 % of cases of cervical cancer are associated with HPV (Soto-Fuenzalida *et al.*, 2020). That´s why, Mexico is

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recognized as one of the American regions with a high rate of HPV infection (Bruni *et al.*, 2021) which may get worse if population has low consumption of fruit and vegetables. Evidence of this was published in 2016 by a Mexican survey which reported that only 51.4 % and 42.3 %, and 47 % and 34.6 % of the population consumed fruits and vegetables, at national level and northern region, respectively (Secretaría de Salud, 2016). Since research on this topic is limited in Mexico, the present study investigated the role of the personal, lifestyle, clinical history, socioeconomic, and antioxidant status to the presence of HPV-infection in adult women from a community of the northwest region of Mexico.

MATERIAL AND METHODS

Participants and study design

This study was performed with women at the George Papanicolaou Group (GPG) founded to care, monitor and support cancer patients; and a hospital institute (Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado de Sonora, ISSSTESON) both set at the state of Sonora (northwest region of Mexico), to investigate the associated risk factors to HPV infection. Sonora is bordering to the east with the state of Chihuahua, south to the state of Sinaloa and north to the state of Arizona of the United States.

It was a case-control study matched by age (± 5 years) conducted from November 2015 to July 2017. Thirty-three women with HPV infection and 66 controls matched (1: 2) for age with or free of HPV infection respectively confirmed by hybrid capture result and history records, agreed to participate. The common eligibility criteria for both cases and matched controls was not being pregnant or lactating at the time of recruitment.

The Ethic Committees of the Centro de Investigación en Alimentación y Desarrollo, A.C. (CIAD A.C), GPG and ISSSTESON approved all procedures involved in this study. All participants signed an informed consent before work began.

Study measurements

Standing height was measured using a stadiometer (Holtain Ltd., Dyfed, UK) with 2.05 ± 0.001 m capacity. Weight was measured (to the nearest 10 g) using a digital electronic scale (AND FV-150 KA1, A&D Co. Ltd., Toshima-ku, Tokyo, Japan) according to standardized recommendations. Weight and height were then used to estimate the Body Mass Index (BMI, kg/m^2). The reference values are normal for BMI >18.5 - 24.9, overweight for BMI ≥ 25 - 29.9, and obesity for BMI ≥ 30 - 34 (CDC, 2022).

A 90-item food-frequency questionnaire (FFQ) designed and validated to estimate usual food consumption in a Mexican women population of low socioeconomic status, age 15 - 54 years, was used in this study. This FFQ was adapted to the population of Sonoran women (Romieu *et al.*, 1999; Quizán-Plata y Ortega, 2000). Participants were asked to report the consumption frequency for each food item during the past year. Results were expressed as g/day.

Exfoliated cells from the cervical canal were collected by an obstetrician. All samples were correctly packed and shipped to the GPG and ISSSTESON laboratories for processing within 48 h. The HPV test was performed in the Laboratorio Estatal de Salud Pública using the Hybrid Capture II (HC2 Digene Corp., Qiagen) to detect oncogenic HPV sub-types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. The analytical sensitivity of the Combined-Probe Cocktail Method is 97.5, with a specificity of 84.3 (PAHO, 2019).

Collection of information and biological samples

Personal, lifestyle, clinical history and socioeconomic information of the participants was collected by using questionnaires, and also blood samples were taken. These activities were carried out in the GPG and ISSSTESON facilities.

Personal: Marital status was categorized as married (0) or unmarried (1). Occupational status was assigned (0) for employed or (1) for unemployed (including homemaker). Age at menarche was assigned as (0) if ≥ 12 years or (1) if < 12 years. The number of previous pregnancies was assessed as (0) for ≤ 1 pregnancy or (1) for > 1 pregnancies.

Lifestyle: Age at first sexual intercourse was (0) for ≥18 years or (1) for < 18 years. The total number of sexual partners in the lifetime was classified as (0) for ≤ 1 sexual partners or (1) for >1 sexual partners, while the total number of sexual partners in the last year was assigned as (0) for ≤ 1 or (1) for > 1. The use of barrier contraceptives was coded as (0) for condom alone or accompanied by another method (Intrauterine device, injection, vasectomy, rhythm and tablets), or (1) when intrauterine device, injection, vasectomy, rhythm, abstinence or tablets were reported (Winer *et al.*, 2006). Use of oral contraceptives was assigned (0) for ≤ 6 years or (1) for > 6 years. Active smoking was scored as (0) for non-smokers or (1) for reports of smoking at least 1 cigarette per day/week. Passive smoking was assigned as (0) when the subject was not exposed to tobacco smoke regularly/sporadically during the past year or (1) when she was exposed.

Clinical history: The presence of sexually transmitted diseases (STDs), such as trichomoniasis, herpes simplex, condyloma acuminate, syphilis, gonorrhea, hepatitis B or chlamydia, was assessed as (0) when not reported or (1) when reported. Finally, type 2 diabetes confirmed by medical records was classified as (0) absent or (1) present.

Socioeconomic: Socioeconomic status (SS) was evaluated using a questionnaire from the Mexican Association of Market Intelligence and Public Opinion (AMAI) (López-Romo, 2009), which applies the following classification: A/B (wealthy), C+ (income or standard of living slightly above average), C (average income and standard of living), D+ (income or standard of living slightly below average), D- (low income and standard of living), and E (lowest income and standard of living). The SS was categorized as either low level (D+ and D-), classified as (1), or high-medium level (A/B, C+, C), assessed as (0).

Blood collection: During visits to the participants, and after an overnight fast, a 10 - mL blood sample was taken

by venipuncture in BD vacutainer tubes (Becton Dickson of 21 G x 38 mm). Samples were transported to CIAD A.C. to separate plasma by centrifugation (ThermoFisher Scientific. Laboratory Centrifuge. Germany, 2016) at 5000 x *g* for 10 min at 4 °C, within 2 h of collection and stored as aliquots in properly labeled 1.5 mL amber Eppendorf tubes at - 80°C until analysis. The entire process was performed under conditions of light protection. TAC was determined using the Randox® NX2332 commercial reagent kit (UK, 2016) following the manufacturer's instructions (Jozanov-Stankov *et al.*, 2009).

Statistical analysis

An exploratory analysis was performed to describe the variables and create new dichotomous or polychotomous variables. Means and standard deviations were estimated for the continuous variables while medians were estimated for the antioxidant nutrient intakes. Prevalence was estimated for all categorical variables. All antioxidant intakes were total energy-adjusted using the residual method (Willett, 1998). In addition, plausible biological variables with OR ≠ 1 and p ≤ 0.2 were selected by univariate logistic regression. Selected variables were analyzed by the multivariate logistic regression to generate the models. Then, the variables in the preliminary models were evaluated for interaction (p ≤ 0.05), collinearity (r > 0.8) and linearity. All data were analyzed using the STATA/SE version 12.0 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

RESULTS

Baseline characteristics between groups

This age-matched, case-control study of 99 women (mean age 41.8 ± 7.9 years, range: 23-56 years old) from northwest Mexico, explored the differences between the control and case (HPV-infection) groups regarding all variables in this study (Tables 1 and 2). No differences were found in age, weight, height, BMI and personal and socioeconomic factors ($p > 0.05$) between the study groups ($p > 0.05$) (Table 1).

An unadjusted analysis failed to detect any difference in the age at menarche (unadjusted OR = 1.84, 95 % CI = 0.798 - 4.295, $p = 0.156$), or age at first sexual intercourse (≥ 18 years) (unadjusted OR = 1.5, 95% CI = 0.575 - 3.912, $p = 0.407$) between groups. The women with more than one pregnancy (unadjusted OR = 6.1, 95 % CI = 2.0 - 18.1, $p = 0.001$), and those with more both sexual partners (unadjusted OR = 2.4, 95 % CI = 1.0 - 6.08, $p = 0.048$), and annual sexual partners (unadjusted OR = 5.9, 95 % CI = 2.2 - 16.1, $p = 0.001$), had a higher probability of being HPV-positive. Also, the women who used oral contraceptives for more than 6 years (unadjusted OR = 3.3, 95 % CI = 1.0 - 11.2, $p = 0.047$), and smoked tobacco (unadjusted OR = 3.9, 95 % CI = 1.3 - 11.5, p = 0.011) or being passive smoking (unadjusted OR = 2.0, 95 % CI = 1.0 - 5.6, p = 0.049) were more likely to have HPV infection. Finally, women with other STDs were 6.9 more likely (95 % CI =1.4 - 22.7, $p = 0.016$) to be HPV-infected.

The categories 'previous type 2 diabetes' and 'vitamin supplementation' were not found to be associated with HPV infection (Table 1). Overall energy-adjusted antioxidant intakes were not associated with HPV infection (Table 2). However, energy-adjusted retinol and lycopene intakes tended to be higher in controls than in cases (OR = 0.95, 95 % CI = 0.8- 1.0, $p = 0.080$: OR = 0.99, 95% CI = 0.999 - 1.000, $p = 0.074$ respectively). Women with higher TAC were less likely to have HPV infection (OR = 0.05, 95% CI = 0.01-0.5, $p = 0.013$).

Biological plausible variables to HPV infection

The variables with OR ≠1 and $p \leq 0.2$ selected for simple logistic regression analysis and with biological plausibility for the risk of HPV infection were number of pregnancies, number of sexual partners, total annual sexual partners, use of oral contraceptives for ≥ 6 years, active tobacco smoking, passive smoking, other STDs, and energy, retinol and lycopene intakes, and TAC (Table 3).

Generation of models

The stepwise analysis generated Model 1 shown in Table 4. Women with more pregnancies (adjusted OR = 5.5, 95 % CI = 1.2 - 28.1, $p = 0.029$) and those with more sexual partners and total annual sexual partners remained in the model, and were more likely to have HPV infection. In contrast, higher consumption of energy-adjusted lycopene (adjusted OR = 0.96, 95 % CI = 0.95 - 0.99, $p = 0.019$) reduced the risk of HPV infection in these women. No interaction ($p \leq 0.05$) or collinearity (r < 0.8) was found between the independent variables.

The stepwise analysis also produced Model 2, and the variables which remained were number of pregnancies, total annual sexual partners and TAC (Table 5). The first two non-nutrient variables were also selected in Model 1. Here, higher TAC status (adjusted OR = 0.05, 95 % CI = 0.03 - 0.7, $p = 0.024$) was related to a reduced risk of HPV infection in participants. Again, no interaction ($p \leq 0.05$) or collinearity (r < 0.8) was found between the independent variables, though linearity was observed in the natural logarithm of HPV infection [P / 1-P] *vs*. TAC when this latter was considered as a categorical variable. A value for TAC above 1.30 mmol/L decreased the probability of HPV infection.

DISCUSSION

A high risk of HPV infection in women with high parity was observed in this study. Mukhopadhyay (2019) also published the association between HPV infection and increased parity in 171 women. It was suggested that in multiparous women, increased hormone levels may result in exposing the ectocervix for a longer period, and the impaired immune response facilitates the settlement of HPV infection. However, de Farias *et al.* (2021) did not find this association (p < 0.05) in women older than 25 years old from a total of 428 participants. Similarly, Liang *et al.* (2018) and Pandey *et al.* (2019) published the same finding in 198 and 101 women, respectively. Although de Farias *et al.* (2021) did not argue their results, the last two attributed to their small sample size, the lack of association.

Table 1. Comparison of the characteristics of the participants with HPV-infection, controls and cases.
Tabla 1. Comparación de las características de los participantes con infección por HPV, controles y casos.

Variable	Controls (n = 66)	Cases (n = 33)	OR (95 % CI)	[c]*p*-value
[a]**Age** (years) (matched factor)	42.2 (± 8.1)	41.0 (± 7.8)	0.66 (0.40 - 1.09)	0.106
[a]**Weight** (kg)	73.7 (± 13.2)	71.2 (± 13.8)	0.98 (0.94 - 1.01)	0.303
[a]**Height** (cm)	1.59 (± 0.058)	1.60 (± 0.06)	0.82 (0.001 - 800.5)	0.956
[a]**BMI**	28.9 (± 5.04)	27.7 (± 5.12)	0.95 (0.87 - 1.04)	0.317
Demographic data				
[b]Marital Status				
Married	45 (68.2 %)	23 (69.7 %)	1.0	
Single/Divorced/Widow	21 (31.8 %)	10 (30.3 %)	0.81 (0.30 - 2.10)	0.678
[b]**Occupation**				
Manual labor/Retired/Professional/Merchant	33 (50 %)	16 (48.5 %)	1.0	
Housewife	33 (50 %)	17 (51.5 %)	1.10 (0.45 - 2.7)	0.822
[b]Socioeconomic Status				
Wealthy	19 (28.8 %)	12 (36.4 %)	1.0	
Average standard of living	18 (27.3 %)	7 (21.2 %)	0.51 (0.15 - 1.8)	0.296
Below average standard of living	19 (28.8 %)	6 (18.2 %)	0.41 (0.11 - 1.51)	0.184
Lowest average standard of living	10 (15.2 %)	8 (24.2 %)	1.31 (0.40 - 4.3)	0.652
[b]Biological data				
Age at menarche				
≥ 12 years	50 (75 %)	21 (63.7 %)	1.0	
< 12 years	16 (25 %)	12 (36.4 %)	1.69 (0.71 - 4.0)	0.235
[b]**Lifestyle**				
Number of previous pregnancies				
0 - 1	45 (68.2 %)	9 (27.3 %)	1.0	
> 1	21 (31.8 %)	24 (72.7 %)	6.1 (2.0 - 18.1)	0.001
Age at first sexual intercourse				
≥ 18 years	50 (76 %)	22 (67 %)	1.0	
< 18 years	16 (24 %)	11 (33 %)	1.7 (0.62 - 4.49)	0.308
Number of sexual partners				
0 - 1	50 (75 %)	18 (55 %)	1.0	
> 1	16 (25 %)	15 (45 %)	2.4 (1.0 - 6.08)	0.048
Total annual sexual partners				
0 - 1	50 (76 %)	10 (30 %)	1.0	
> 1	16 (24 %)	23 (70 %)	5.9 (2.2 - 16.1)	0.001
Use of condom alone and other methods (Intrauterine device, injection, vasectomy, rhythm, tablets)				
No	37 (56 %)	20 (60 %)	1.0	
Yes	29 (44 %)	13 (40 %)	0.79 (0.31 - 2.0)	0.636
Oral contraceptives for ≥ 6 years.				
No	56 (85 %)	22 (67 %)	1.0	
Yes	10 (15 %)	11 (33 %)	3.3 (1.01 - 11.2)	0.047
Active tobacco smoking				
No	60 (91 %)	22 (67 %)	1.0	
Yes	6 (9 %)	11 (33 %)	3.9 (1.3 - 11.5)	0.011
Passive smoking				
No	45 (68 %)	16 (49.5 %)	1.0	
Yes	21 (32 %)	17 (51.5 %)	2.036 (1.0 - 5.6)	0.049
Disease				
Other STDs				
No	63 (95 %)	25 (76 %)	1.0	
Yes	3 (5 %)	8 (24 %)	6.9 (1.4 - 22.7)	0.016
Previous type 2 diabetes				
No	57 (86 %)	27 (82 %)	1.0	
Yes	9 (14 %)	6 (18 %)	1.4 (0.4 - 4.6)	0.542
Vitamin-Supplementation				
Yes	50 (76 %)	27 (82 %)	1.0	
No	16 (24 %)	6 (18 %)	0.5 (0.17 - 1.8)	0.366

[a]Mean values with standard deviation
[b]Number of participants and percentage
[c]Conditional logistic regression analysis
OR = Odds Ratio; BMI = Body Mass Index; STDs = Sexual Transmitted Diseases; OR = Odds ratio; CI = 95 % Confidence Interval; p = Significant level $p < 0.05$.

Table 2. Association of nutrient antioxidants intake and TAC with HPV-infection in controls and cases.
Tabla 2. Asociación de la ingesta de nutrientes antioxidantes, y TAC con infección por HPV en controles y casos.

[a]Dietary nutrients	Controls (n = 66)	Cases (n= 33)	OR (CI)	[c]*p* - value
Energy (kcal/d)	2040 (1875.8 - 2305.5)	1710 (1579.6 - 1833.9)	0.998 (0.97 - 0.99)	0.025
Vitamin C (mg/d)	136.8 (110.2 - 154.5)	122.7 (89.3 - 167.8)	1.0 (0.99 - 1.0)	0.889
Vitamin A (RE/d)	761.0 (634.5 - 850.9)	673.5 (577.3 - 784.8)	1.0 (0.99 - 1.0)	0.745
Retinol (µg/d)	266.5 (222.2 - 304.7)	259.9 (187.8 - 334.8)	0.95 (0.8 - 1.0)	0.080
α-carotene (µg/d)	1015.5 (928.4 - 1052.4)	976.6 (792.7 - 1030.7)	1.0 (0.99 -1 .01)	0.889
β-carotene (µg/d)	3840.2 (3215.1 - 4236.8)	3561.4 (2995.9 - 4314.4)	0.99 (0.99 - 1.0)	0.207
β-cryptoxanthin (µg/d)	288.3 (195.6 - 325.8)	300 (193.1 - 380.3)	1.0 (0.99 - 1.00)	0.251
Lycopene (µg/d)	3350.9 (2665.6 - 4233.7)	2692.5 (1845 - 3838.6)	0.97 (0.95 - 1.0)	0.079
Lutein-zeaxanthin (µg/d)	1501.8 (1190.3 - 2108)	1475.2 (850-2238.2)	0.9 (0.999 - 1.000)	0.712
Vitamin E (mg/d)	5.6 (5.1 - 6.4)	5.0 (4.1 - 5.5)	1.03 (1.0 - 1.05)	0.012
α-tocopherol (mg/d)	5.6 (5.1 - 6.2)	5.0 (4.0 - 5.5)	1.05 (1.0 - 1.09)	0.013
β-tocopherol (mg/d)	0.17 (0.15 - 0.20)	0.13 (0.10 - 0.21)	18.4 (0.12 - 2.7)	0.253
γ-tocopherol (mg/d)	4.14 (3.3 - 5.4)	3.9 (3.3 - 5.1)	0.94 (0.81 - 1.1)	0.504
[b]Blood nutrients				
TAC (mmol/L)	1.39 (0.29)	1.21 (0.25)	0.06 (0.01-0.6)	0.013

[a]Median values and interquartile range. Nutrients were energy-adjusted by the residual method
[b]Mean values with standard deviation
[c]Conditional logistic regression analysis
OR = Odds Ratio; TAC = Total Antioxidant Capacity in plasma; p = Significant level $p < 0.05$.

Table 3. Plausible biological variables selected by simple logistic regression analysis.
Tabla 3. Variables biológicas plausibles, seleccionadas mediante análisis de regresión logístico simple.

HPV infection	OR	95 % CI	[b]*p*-value
Number of previous pregnancies	6.1	2.0 - 18.1	0.001
Number of sexual partners	2.4	1.0 - 6.1	0.048
Total annual sexual partners	5.9	2.2 - 16.1	0.001
Oral contraceptives for ≥ 6 years.	3.3	1.0 - 11.2	0.047
Active tobacco smoking	3.9	1.3 - 11.5	0.011
Passive smoking	2.04	1.0 - 5.6	0.049
Other STDs	6.9	1.4 - 22.7	0.016
[a]Energy (kcal/d)	0.99	0.97 - 0.99	0.016
[a]Retinol (µg/d)	0.9	0.8 - 1.0	0.080
[a]Lycopene (µg/d)	0.97	0.95 - 1.0	0.079
TAC (mmol/L)	0.05	0.01 - 0.5	0.013

[a]Nutrients were energy-adjusted by the residual method
[b]Simple logistic regression analysis
OR = Odds Ratio; CI = 95 % Confidence Interval; STDs = Sexual Transmitted Diseases; TAC = Total Antioxidant Capacity in plasma; p = Significant level $p < 0.05$.

Table 4. Factors associated with HPV-infection identified by conditional multiple logistic regression (Model 1).
Tabla 4. Factores asociados con la infección por HPV, identificados mediante regresión logística múltiple condicionada (Modelo 1).

Variable	SE	OR	95 % CI	*p*-value
Number of previous pregnancies	4.6	5.5	1.2 - 28.1	0.029
Number of sexual partners	9.7	10.8	2.9 - 58.7	0.01
Total annual sexual partners	4.9	5.9	1.5 - 25.5	0.023
[a]Lycopene (µg/d)	0.003	0.96	0.95 - 0.99	0.019

[a]Antioxidant nutrients were energy-adjusted by the residual method
SE = Standard Error; OR = Odds Ratio; CI = 95 % Confidence Interval; p = Significant level $p < 0.05$.

Table 5. Factors associated with HPV-infection identified by conditional multiple logistic regression (Model 2).
Tabla 5. Factores asociados con la infección por HPV, identificados por regresión logística múltiple condicionada (Modelo 2).

Variable	SE	OR	95 % CI	*p* - value
Number of previous pregnancies	7.63	9.26	1.88 - 45.44	0.01
Total annual sexual partners	4.16	6.45	1.82 - 22.85	0.01
TAC (mmol/L)	0.065	0.05	0.03 - 0.7	0.024

SE = Standard Error; OR = Odds Ratio; CI = 95 % Confidence Interval; TAC= Total Antioxidant Capacity in plasma; p = Significant level $p < 0.05$.

Women with more sexual partners and annual sexual partners were at higher risk of HPV infection. Itarat *et al.* (2019) found that women (n = 349) with multiple sexual partners had a higher risk of HPV as compared with those with limited sexual partners. However, authors recognized that lack of information about the HPV duration and sexual behavior of the partners of the recruited women was a limitation to provide a better conclusion.

The consumption of lycopene and a better TAC reduced the risk of HPV infection in our study. No association was found between the consumed antioxidants and those in plasma (data not shown), and it was observed that nutrient antioxidant supplementation was similar ($p = 0.496$) in both groups. Pellegrini *et al.* (2018) concluded that different studies explain the reasons to understand the limitation to recognize the plasma TAC as a biomarker of dietary antioxidant intake. One of them is that antioxidants in plasma may influence the antioxidant compounds in other biological fluids; and second, the little understanding of the high inter-individual variability given by TAC assays, as a result of the unnoticed contribution by antioxidant enzymes. On the other hand, Barchitta *et al.* (2020) reported that 251 women with high antioxidants intake (zinc, selenium, manganese, vitamin A, vi-

tamin C, vitamin E, carotenoid, and flavonoids) were at lower risk of HPV infection. A recent review by Ono *et al.* (2020) described that intake of vitamins A, D and carotenoids such as lycopene, may inhibit early events of cervical cancer from HPV infection, but the mechanisms of action remain unclear. On the other hand, Lin *et al.* (2021) reported that women with the lowest antioxidant serum levels had a higher risk of HPV infection from 11,070 women aged 18 - 59 who participated in the 2003 - 2016 National Health and Nutrition Examination Survey in USA.

CONCLUSION

Women with more pregnancies and sexual partners were at higher risk of HPV infection. On the other hand, higher dietary consumption of lycopene and TAC in blood reduced the risk of HPV infection in this study. The strength of this research lies in its matched case-control design, all the study variables explored, and the information generated about a largely unexplored topic in a Mexican population. However, the sample size and the absence of information on the role of male partners in HPV infection transmission were a limitation of this study. On the other hand, although the sexual intercourse at early age was not associated to HPV infection, a high percentage of our participant women reported had sexual intercourse before the age of 18. This finding may lead to the National Ministry of Health to look over the valid cervical cancer standards to lower the age for the HPV infection diagnosis in Mexican women. Strengthening both the sexual education and the increase of antioxidants consumption in women, at least at local level, to prevent the development of cervical cancer should be carried out.

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