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Association between Type-2 Diabetes Mellitus and Infection by Human Papillomavirus Genotype-18 in Women Aged 40-44 Years Old

Daniel López-Hernández [a*], Tania Castillo-Cruz [b], Leticia Brito-Aranda [c], Luis Beltrán-Lagunes [d], Nadhyieli Orozco-Campos [e] and Emanuel Melgarejo-Estefan [f]

[a] Quality Management Coordination, Family Medicine Clinic "División del Norte", The Security Institute and Workers' Social Services of the State, North Division Avenue Number 3755, San Pablo Tepetlapa, Coyoacan, C.P. 04840, Mexico City, Mexico.
[b] Medical Coordination, Family Medicine Clinic "División del Norte", The Security Institute and Workers' Social Services of the State, North Division Avenue Number 3755, San Pablo Tepetlapa, Coyoacan, C.P. 04840, Mexico City, Mexico.
[c] Centro de Investigación y Educación Continua, S.C. La Perla, Nezahualcóyotl, C.P. 57820, Mexico State, Mexico.
[d] Teaching and Research Service, Family Medicina Clinic "Gustavo A. Madero", The Security Institute and Workers' Social Services of the State, Calzada Guadalupe Number 712, Tepeyac Insurgentes, Gustavo A. Madero, C.P. 07020, Mexico City, Mexico.
[e] Physician, Family Medicina Clinic "Narvarte", The Security Institute and Workers' Social Services of the State, Eugenia Street Number 230, Narvarte Poniente, Benito Juárez, C.P. 03020, Mexico City, Mexico.
[f] Health Regulations Directorate, The Security Institute and Workers' Social Services of the State, San Fernando Avenue Number 547, San Fernando, Tlalpan, C.P. 14070, Mexico City, Mexico.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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**Corresponding author: E-mail: daniel16042016@gmail.com, ceninvec@gmail.com;*

ABSTRACT

Objective: To analyze the prevalence and incidence of Human Papillomavirus (HPV) infection and its possible association with type 2 diabetes mellitus.
Materials and Methods: A retrospective cohort study was conducted. Exposure was HPV-infection.
Results: 13234 females were analyzed [median of age=46], 1215 cases of diabetes (median of age=53) and 12019 cases without diabetes (median of age=45). There were 1495 (11.3%; 95%CI 10.8–11.8) new cases of HPV infection by any genotype, 234 (1.8%; 95%CI 1.5–2.0) by genotype-16, 102 (0.8%; 95%CI 0.8–0.8) by genotype-18, and 1279 (9.7%; 95%CI 9.2–10.1) by high risk (HR) genotypes. The global crude-prevalence by any genotype, and HR-genotypes was significantly lower (p=0.008) in subjects with diabetes compared with their counterparts without diabetes. The mean duration of follow-up was 1.1 years. The global crude-incidence rate of HPV-infection per 1000 person-years by any genotype, and genotypes-16, - 18, and -HR was 99.36, 15.55, 6.78, and 85.01, respectively. The crude hazard ratio of infection by HPV-18 genotype was higher in women with diabetes and age between 20-24y (HR=36.611; 95%CI 4.009-334.303, p=0.001), and 40-44y (HR=3.947; 95%CI 1.124-13.857, p=0.032) compared with their counterparts without diabetes.
Conclusion: Type 2 diabetes mellitus increases the risk of infection by HPV-genotype-18 in young adult woman.

Keywords: Human papillomavirus infection; human papillomavirus genotypes; diabetes mellitus.

1. INTRODUCTION

Diabetes is a pandemic disease that affects more than 422 million adults (2014), and caused 1.6 million deaths in 2016 [1]. In general, infectious diseases are more frequent and serious in patients with diabetes. Potentially, increases both morbidity and mortality [2]. Patients with diabetes have a greater risk of infection in lower respiratory tract, urinary tract, skin, and mucous membrane (bacterial and mycotic infection), and the risks increased with recurrences of common infections [3]. Even more, the greater frequency of infections in people with diabetes is associated to hyperglycemic environment that favors immune dysfunction (e.g., damage to the neutrophil function, depression of the antioxidant system, and humoral immunity) [2]. Moreover, people with diabetes are more predisposed to skin and soft tissue infections (such as folliculitis, furunculosis, and subcutaneous abscesses), tuberculosis infection, respiratory infections, acute pyelonephritis, perinephric and/or renal abscesses, emphysematous pyelonephritis, renal papillary necrosis, and viral infection such as hepatitis C, immune immunodeficiency virus, and enterovirus (especially Coxsackie B4 and B3 virus) [4-5].

Additionally, clinical and epidemiological association between type 2 diabetes mellitus (t2DM) and human papillomavirus (HPV) infection is virtually scarce. The association of these two clinical conditions poses a major burden to the health public system, especially in the developed countries where HPV is an important cause of sexual infection and the prevalence of t2DM is increasing. In low- and middle-income countries, the prevalence of cervical cancer (CC) in women with t2DM was significantly higher compared with females without diabetes [6].

Moreover, it's necessary a study on the risk of HPV infection in patients with t2DM for clinical consultations and HPV control policy decisions.

2. MATERIALS AND METHODS

2.1 Dataset and Data Selection

A population-based retrospective cohort study was designed, which is nested within two programmes from "The Security Institute and Worker's Social Services of the Sate": 1) the prevention programme for non- communication chronic disease (NCCD) and 2) the screening programme for HPV infection and CC (HPV-CC). The HPV-CC programme contains all dataset of women who had a negative or positive HPV test recorded by the Institutional public health laboratories and gynecological and obstetrics medical information. Individuals were matched (by age and sex) to the dataset of prevention programme-NCCD which has sociodemographic information for each patient (men and women), medical personal history of NCCD and anthropometrics measures. For this analysis, we

used a subset from prevention programme-NCCD, and from HPV- CC programme, limited to women who entered the dataset after Jan 1st, 2011. Records with an invalid or missing date, or result were removed. We included all women with a follow-up in December 31st, 2014. All data sources were linked by the use of a Central Person Registry number. During this period, diagnostic method for detection of samples with HPV infection were equal between laboratories. The data collection was designed according to a retrospective cohort to examine the association between exposure status (diabetes) and the outcome (HPV infection).

2.2 Molecular and Sampling Procedures for Detection of Human Papillomavirus Infection

The molecular detection of HPV DNA was performed using an automated sample preparation system. The system uses amplification of target DNA by the technics of PCR and nucleic acid hybridization, for detecting 14 high-risk (HR) HPV-genotypes in a single analysis. The genotypes of HPV identified are the genotypes 16 and 18 (HPV-16 and HPV-18), and a pool of other HR-HPV genotypes: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

2.3 Outcome and Study Variables

The prevention programme-NCCD contains data on smoking history, personal medical history of diabetes, hypertension, obesity and cancer (for women: cervical cancer and breast cancer, and for men: prostate cancer). All cases of t2DM were diagnosis, by physicians of prevention programme, in line with American Diabetes Association recommendations. The HPV-CC programme contains data on medical history of gynecological and obstetrics clinical condition, background of Pap smear and PCR test. According to the hypothesis that t2DM increases the risk of HPV infection, there were only included women who underwent to PCR testing after their diagnosis of t2DM. Women who underwent to PCR testing before their diagnosis of t2DM, were excluded.

2.4 Statistical Analysis

Categorical variables were described by both, the absolute frequency, and percentage with the corresponding 95% confidence interval (CI). All categorical variables were compared using chi square test. Prevalence of HPV infection was defined as the number of women with these diagnoses by the end of follow-up divided by the number of women at baseline, and incidence rate of HPV infection was defined as the number of women diagnosed with this infection divided by person-time. To calculate the incidence density rate ratio, we calculated the incidence ratio by both diabetes and non-diabetes group. The primary aim was to test if there is an increase on the risk of HPV infection with both exposures: to t2DM and glucose levels. The crude and adjusted odds ratio (OR), and their corresponding 95% CI were estimated using conditional logistic regression models, controlling for potential confounders. The Kaplan–Meier method was used to estimate cumulative risk of HPV infection. Hazard ratios (HRs) were estimated using Cox proportional hazard models. The proportionality of hazards was verified by modeling that showed no statistically significant change in hazard ratios with increasing follow-up time. The period of person years was measured from study entry to time of HPV diagnosis for all women who developed the infection or from study entry until December 31st, 2014 for women without HPV infection. All statistical tests were two-sided. A p value < 0,05 (2- sided testing) was considered significant.

3. RESULTS

A total of 13234 women (matched from both dataset) were included [Median of age= 46 years old; Interquartile range (IQR)= 38-52], 1215 cases of diabetes (median age 53 years, IQR 47-59 years) and 12019 cases without diabetes (median age 45 years, IQR 37-52 years).

There were 1495 (11.3%; 95% CI 10.8–11.8) new cases of HPV infection by any genotype, 234 (1.8%; 95% CI 1.5–2.0) by genotype 16, 102 (0.8%; 95% CI 0.8–0.8) by genotype 18, and 1279 (9.7%; 95% CI 9.2–10.1) by high-risk genotypes.

The mean age at cohort entry was 45.4 years (SD 10.4; range 16.0–85.0), mean duration of follow-up was 1.1 years (median 1.0 years, range 1 day to 3.6 years, IQR 0.2–1.8), and total duration of follow-up was 15045.8 person-years.

The global crude prevalence of HPV infection by any genotype, was 11.3%. This prevalence was significantly lower (p= 0.008) in subjects with diabetes compared with their counterparts without diabetes (Table 1). Similarly, the

prevalence of infection by HR-HPV genotypes was significantly lower in the same group. Additionally, the prevalence of infection by both 16-, and 18-HPV genotypes was similar in both groups (Table 1).

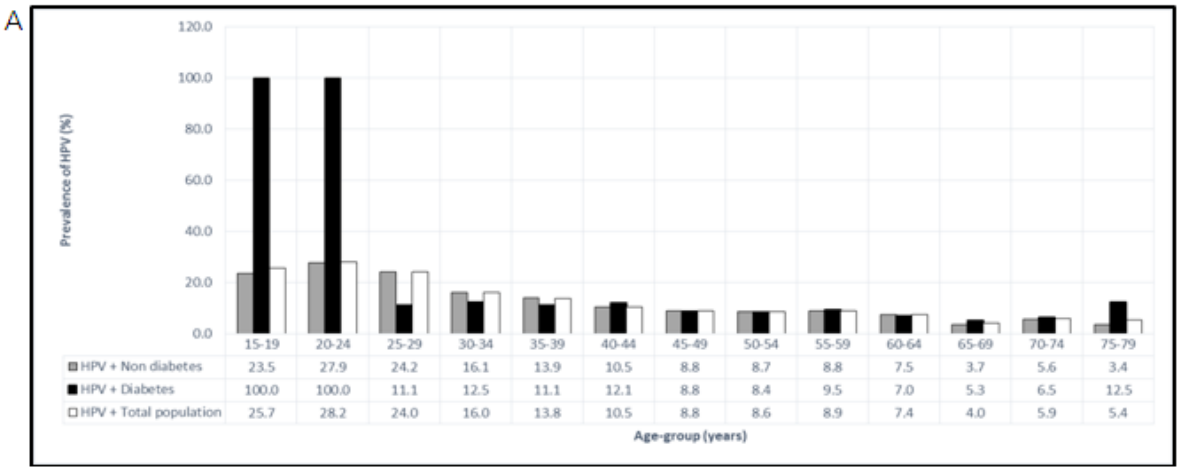
As shown in Fig. 1, for overall population, HPV prevalence estimates were the highest in women in the 20-24 year-group (69, 28.2%; 95% CI 22.9–33.9), and prevalence decreased in the 65-69 year-group (10, 4.0%; 95% CI 2.6–5.0). Moreover, there were not cases of infection by genotypes 16, and 18 and HR in several age-groups.

Table 1. Prevalence and incidence of human papillomavirus infection of the total study population, by genotypes

Prevalence				
Variables	**Total population N=13234**	**Group with diabetes n= 1215**	**Group without diabetes**	***P Value***
	N; % (CI 95%)	n; % (CI 95%)	n= 12019 n; % (CI 95%)	
Any HPV	1495; 11.3 (10.8-11.8)	109; 9.0 (7.4-10.7)	1386; 11.5 (11.0-12.1)	0.008
HPV-16	234; 1.8 (1.5-2.0)	18; 1.5 (0.8-2.2)	216; 1.8 (1.5-2.0)	NS
HPV-18	102; 0.8 (0.6-0.8)	10; 0.8 (0.4-1.3)	92; 0.8 (0.6-0.9)	NS
HPV-HR	1279; 9.7 (9.2-10.1)	90; 7.4 (6.0-9.0)	1189; 9.9 (89.6-90.6)	0.006

Incidence			
Variables	**New cases of HPV infection**	**Person-years of follow-up**	**Incidence rate[£] (95% CI) per 1000 person-years**
Any genotype	1495	15045·8	99.36 (92.49-106.75)
HPV-16	234	15045·8	15.55 (12.97-18.64)
HPV-18	102	15045·8	6.78 (5.15-8.92)
HPV-HR	1279	15045·8	85.01 (78.67-91.86)

CI: Confidence interval, HPV: Human papillomavirus, HR: High risk, P value, for prevalence, was calculated by Chi square test. [£] Crude incidence rate



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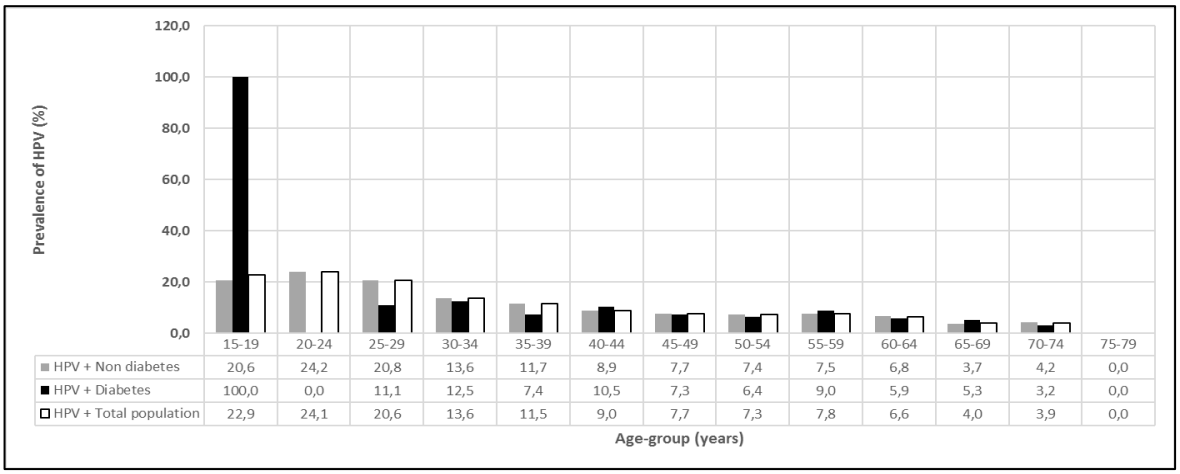
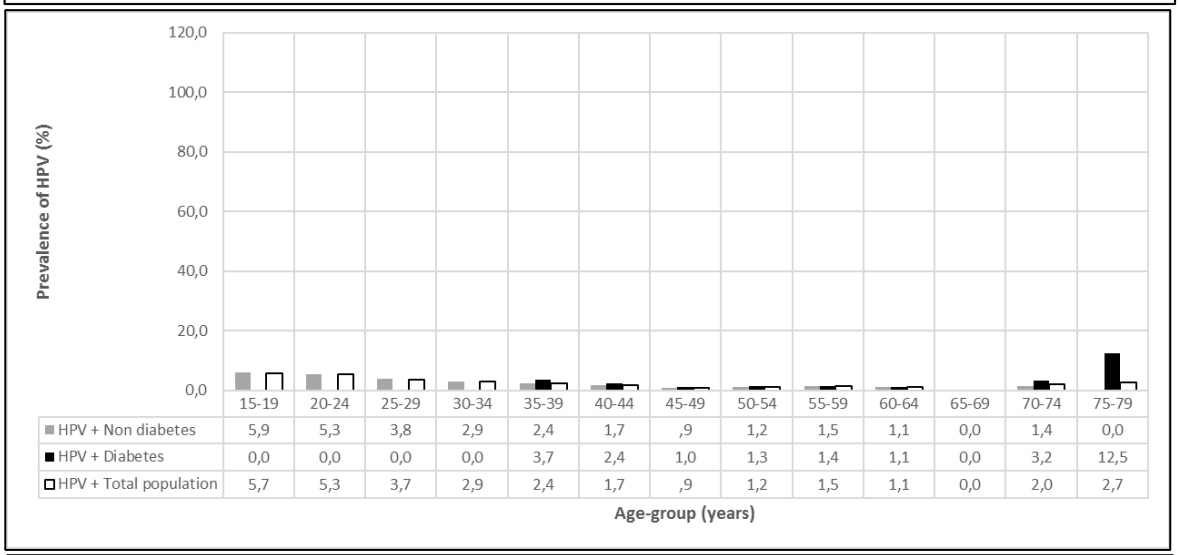


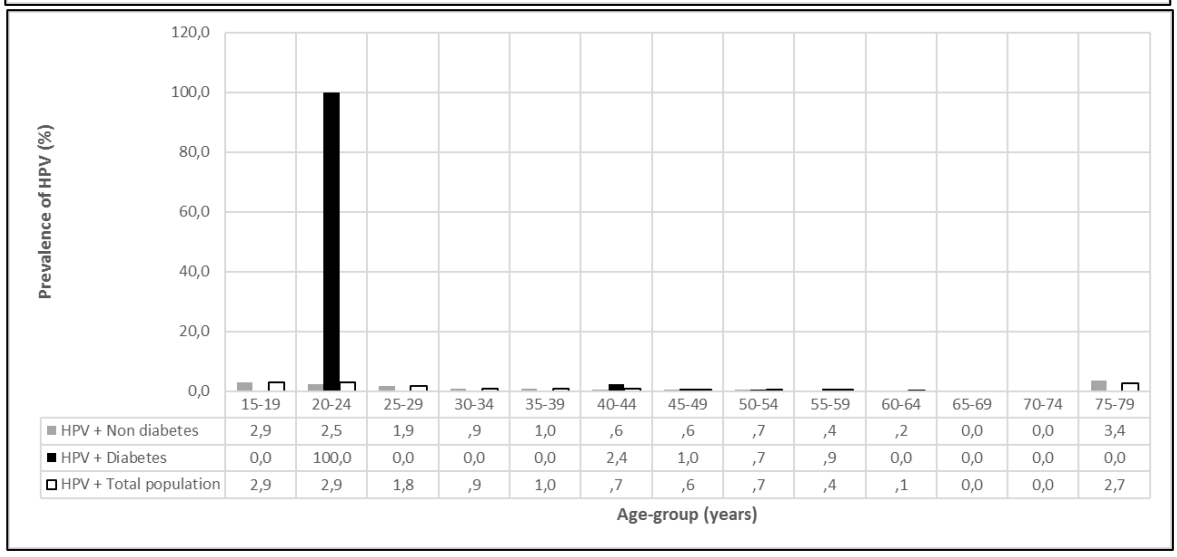
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
HPV + Non diabetes	20,6	24,2	20,8	13,6	11,7	8,9	7,7	7,4	7,5	6,8	3,7	4,2	0,0
HPV + Diabetes	100,0	0,0	11,1	12,5	7,4	10,5	7,3	6,4	9,0	5,9	5,3	3,2	0,0
HPV + Total population	22,9	24,1	20,6	13,6	11,5	9,0	7,7	7,3	7,8	6,6	4,0	3,9	0,0

C



	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
HPV + Non diabetes	5,9	5,3	3,8	2,9	2,4	1,7	,9	1,2	1,5	1,1	0,0	1,4	0,0
HPV + Diabetes	0,0	0,0	0,0	0,0	3,7	2,4	1,0	1,3	1,4	1,1	0,0	3,2	12,5
HPV + Total population	5,7	5,3	3,7	2,9	2,4	1,7	,9	1,2	1,5	1,1	0,0	2,0	2,7

D



	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
HPV + Non diabetes	2,9	2,5	1,9	,9	1,0	,6	,6	,7	,4	,2	0,0	0,0	3,4
HPV + Diabetes	0,0	100,0	0,0	0,0	0,0	2,4	1,0	,7	,9	0,0	0,0	0,0	0,0
HPV + Total population	2,9	2,9	1,8	,9	1,0	,7	,6	,7	,4	,1	0,0	0,0	2,7

Fig. 1. Human papillomavirus prevalence by age-groups

a) Infection with any human papillomavirus genotypes. b) Infection with high-risk human papillomavirus genotypes. c) Infection with human papillomavirus genotype 16. d) Infection with human papillomavirus genotype 18.

Table 2. Incidence of human papillomavirus infection per 1000 person-years, by genotypes

	New cases of any HPV genotype infection		Person-years of follow-up		Incidence rate[£] (95% CI) per 1000 person-years		Incidence density rate ratio (95% CI)
HPV genotype	**Diabetes n= 1215**	**Non-diabetes n= 12019**	**Diabetes**	**Non-diabetes**	**Diabetes**	**Non-diabetes**	
Any genotype							
Total	109	1386	1363.3	13682.5	79.95 (65.79-97.17)	101.30 (83.35-123.10)	0.7893 (0.6495-0.9592)
15-19	1	8	1.2	38.08	833.33 (104.22-6663.02)	210.08 (26.27-1679.75)	3.9667 (0.4961-31.7160)
20-24	1	68	1.2	247.36	833.33 (115.71-6001.67)	274.90 (38.17-1979.85)	3.0314 (0.4209-21.8320)
25-29	1	155	11.2	721.92	89.29 (12.50-637.88)	214.71 (30.05-1533.91)	0.4159 (0.0582-2.9710)
30-34	2	192	20.88	1445.28	95.79 (23.78-385.77)	132.85 (32.99-535.03)	0.7210 (0.1790-2.9039)
35-39	6	223	61.6	1877.04	97.40 (43.29-219.14)	118.80 (52.81-267.29)	0.8199 (0.3644-1.8446)
40-44	15	218	142.88	2505.2	104.98 (62.22-177.15)	87.02 (51.57-146.84)	1.2064 (0.7150-2.0358)
45-49	18	196	262.4	2655.04	68.60 (42.33-111.16)	73.82 (45.56-119.63)	0.9292 (0.5734-1.5058)
50-54	25	173	340.56	2214.88	73.41 (48.26-111.65)	78.11 (51.35-118.80)	0.9398 (0.6179-1.4295)
55-59	21	98	255.84	1168.88	82.08 (51.23-131.50)	83.84 (52.33-134.32)	0.9790 (0.6111-1.5685)
60-64	13	43	178.16	538.48	72.97 (39.24-135.69)	79.85 (42.94-148.50)	0.9138 (0.4914-1.6992)
65-69	3	7	49.68	172.16	60.39 (15.62-233.53)	40.66 (10.51-157.24)	1.4852 (0.3840-5.7434)
70-74	2	4	25.84	69.76	77.40 (14.18-422.58)	57.34 (10.50-313.06)	1.3498 (0.2472-7.3699)
75-79	1	1	8.8	24.72	113.64 (7.11-1816.85)	40.45 (2.53-646.78)	2.8091 (0.1757-44.9127)
80-84	0	0	3.04	3.52	Undetermined	Undetermined	Undetermined
85 and more	0	0	0	0.16	Undetermined	Undetermined	Undetermined
HPV-16							
Total	18	216	1363.3	13682.5	13.20 (8.16-21.36)	15.79 (9.76-25.53)	0.8364 (0.5171-1.3528)
15-19	0	2	1.2	38.08	Undetermined	52.52 (7.40-372.86)	Undetermined
20-24	0	13	1.2	247.36	Undetermined	52.55 (24.36-113.37)	Undetermined
25-29	0	24	11.2	721.92	Undetermined	33.24 (18.88-58.54)	Undetermined
30-34	0	35	20.88	1445.28	Undetermined	24.22 (15.16-38.69)	Undetermined
35-39	2	38	61.6	1877.04	32.47 (7.83-134.58)	20.24 (4.88-83.92)	1.6038 (0.3869-6.6478)
40-44	3	35	142.88	2505.2	21.00 (6.46-68.27)	13.97 (4.30-45.43)	1.5029 (0.4622-4.8866)
45-49	2	21	262.4	2655.04	7.62 (1.79-32.51)	7.91 (1.85-33.73)	0.9636 (0.2259-4.1099)
50-54	4	24	340.56	2214.88	11.75 (4.08-33.85)	10.84 (3.76-31.23)	1.0839 (0.3761-3.1240)
55-59	3	17	255.84	1168.88	11.73 (3.44-40.01)	14.54 (4.26-49.63)	0.8063 (0.2363-2.7512)
60-64	2	6	178.16	538.48	11.23 (2.27-55.62)	11.14 (2.25-55.21)	1.0075 (0.2033-4.9918)

	New cases of any HPV genotype infection		Person-years of follow-up		Incidence rate[£] (95% CI) per 1000 person-years		Incidence density rate ratio (95% CI)
HPV genotype	**Diabetes n= 1215**	**Non-diabetes n= 12019**	**Diabetes**	**Non-diabetes**	**Diabetes**	**Non-diabetes**	
65-69	0	0	49.68	172.16	Undetermined	Undetermined	Undetermined
70-74	1	1	25.84	69.76	38.70 (2.42-618.74)	14.33 (0.90-229.19)	2.6997 (0.1689-43.1635)
75-79	1	0	8.8	24.72	113.64 (7.11-1816.85)	Undetermined	Undetermined
80-84	0	0	3.04	3.52	Undetermined	Undetermined	Undetermined
85 and more	0	0	0	0.16	Undetermined	Undetermined	Undetermined
HPV-18							
Total	10	92	1363.3	13682.5	7.34 (3.82-14.09)	6.72 (3.50-12.91)	1.0909 (0.5680-2.0952)
15-19	0	1	1.2	38.08	Undetermined	26.26 (1.64-419.86)	Undetermined
20-24	1	6	1.2	247.36	833.33 (100.32-6922.11)	24.26 (2.92-201.48)	34.3556 (4.1360-285.3755)
25-29	0	12	11.2	721.92	Undetermined	16.62 (7.47-37.00)	Undetermined
30-34	0	11	20.88	1445.28	Undetermined	7.61 (3.30-17.56)	Undetermined
35-39	0	16	61.6	1877.04	Undetermined	8.52 (4.26-17.05)	Undetermined
40-44	3	13	142.88	2505.2	21.00 (5.98-73.68)	5.19 (1.48-18.21)	4.0462 (1.1530-14.1992)
45-49	2	13	262.4	2655.04	7.62 (1.72-33.78)	4.90 (1.10-21.70)	1.5567 (0.3513-6.8983)
50-54	2	14	340.56	2214.88	5.87 (1.33-25.84)	6.32 (1.44-27.81)	0.9291 (0.2112-4.0881)
55-59	2	4	255.84	1168.88	7.82 (1.43-42.68)	3.42 (0.63-18.68)	2.2844 (0.4184-12.4723)
60-64	0	1	178.16	538.48	Undetermined	1.86 (0.12-29.69)	Undetermined
65-69	0	0	49.68	172.16	Undetermined	Undetermined	Undetermined
70-74	0	0	25.84	69.76	Undetermined	Undetermined	Undetermined
75-79	0	1	8.8	24.72	Undetermined	40.45 (2.53-646.78)	Undetermined
80-84	0	0	3.04	3.52	Undetermined	Undetermined	Undetermined
85 and more	0	0	0	0.16	Undetermined	Undetermined	Undetermined
HPV-HR							
Total	90	1189	1363.3	13682.5	66.02 (53.28-81.79)	86.90 (70.14-107.67)	0.7597 (0.6132-0.9412)
15-19	1	7	1.2	38.08	833.33 (102.52-6773.42)	183.82 (22.62-1494.14)	4.5333 (0.5577-36.8474)
20-24	0	59	1.2	247.36	Undetermined	238.52 (166.26-342.17)	Undetermined
25-29	1	133	11.2	721.92	89.29 (12.48-638.55)	184.23 (25.76-1317.57)	0.4846 (0.0678-3.4660)
30-34	2	163	20.88	1445.28	95.79 (23.75-386.26)	112.78 (27.97-454.80)	0.8493 (0.2106-3.4249)
35-39	4	188	61.6	1877.04	64.94 (24.12-174.82)	100.16 (37.20-269.65)	0.6483 (0.2408-1.7455)
40-44	13	186	142.88	2505.2	90.99 (51.85-159.65)	74.25 (42.31-130.28)	1.2255 (0.6984-2.1503)
45-49	15	172	262.4	2655.04	57.16 (33.73-96.89)	64.78 (38.22-109.81)	0.8824 (0.5206-1.4957)

	New cases of any HPV genotype infection		Person-years of follow-up		Incidence rate[£] (95% CI) per 1000 person-years		Incidence density rate ratio (95% CI)
HPV genotype	**Diabetes n= 1215**	**Non-diabetes n= 12019**	**Diabetes**	**Non-diabetes**	**Diabetes**	**Non-diabetes**	
50-54	19	148	340.56	2214.88	55.79 (34.60-89.95)	66.82 (41.45-107.73)	0.8349 (0.5179-1.3461)
55-59	20	84	255.84	1168.88	78.17 (48.00-127.31)	71.86 (44.13-117.03)	1.0878 (0.6680-1.7715)
60-64	11	39	178.16	538.48	61.74 (31.62-120.55)	72.43 (37.09-141.42)	0.8525 (0.4366-1.6645)
65-69	3	7	49.68	172.16	60.39 (15.62-233.53)	40.66 (10.51-157.24)	1.4852 (0.3840-5.7434)
70-74	1	3	25.84	69.76	38.70 (4.03-372.06)	43.00 (4.47-413.44)	0.8999 (0.0936-8.6515)
75-79	0	0	8.8	24.72	Undetermined	Undetermined	Undetermined
80-84	0	0	3.04	3.52	Undetermined	Undetermined	Undetermined
85 and more	0	0	0	0.16	Undetermined	Undetermined	Undetermined

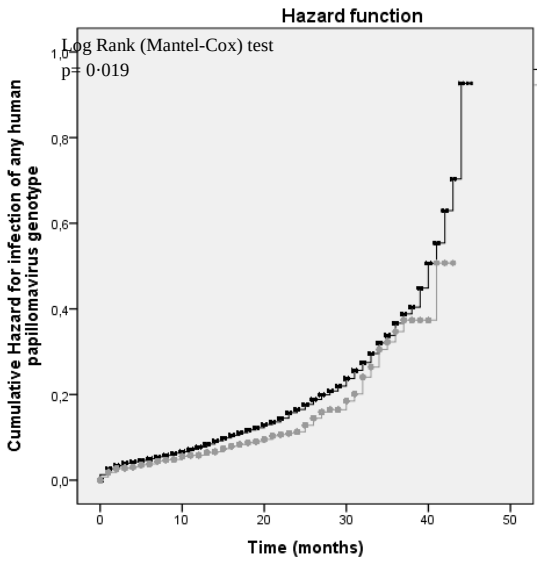
HPV: Human papillomavirus, CI: Confidence interval, HR: High risk. [£] Crude incidence rate. 95% CIs were calculated using logarithmic transformation method

The HPV prevalence by genotypes 16, 18, and HR was the highest in women in the 75–79-year-old-group, in the 20–24-year-old-group, and in the 15–19 year- group, respectively. For women who live with diabetes, there were not cases of HPV infection by genotype 16 in the age-groups between 15 and 34 years. Similarly, there were no cases of infection by genotype 18 in women under 19 years old, in women between 25 and 39 years old, and in women over 60 years old. In relation to infection by HR-HPV genotypes there were not cases in the 20–24-year-old-group. On the other hand, the overall crude incidence rate (CIR) of HPV infection by any genotypes per 1000 person-years is 99.36, 15.55, 6.78 and 85.01 per 1000 person-years by any genotypes, HPV-genotypes 16, 18, and HR, respectively. The highest CIRs (per 1000 person-years) by all genotypes was in women under 30 years old, and this incidence decreased in the 65–69-year-old group. A second peak was observed in the age- groups: 30–34, and 35-39 years old. By genotypes 16, 18, and HR the CIRs of infection per 1000 person-years were the highest in women under 25 years old, and by genotype 18 a second peak was in the 75–79-year-old group. However, the CIRs diminish in different age- groups. The CIR of infection decreased in the 45–49-year-old-group by genotype 16, in the 60–64-year-old-group by genotype 18, and in the 70–74-year-old-group by HR genotypes. A second peak of new cases of infection (by genotypes 16, 18 and HR) in age-group of 25–29 years old was observed. Similarly, in women in the older group between 75 and 79 years old (genotype 16), and in the 30–34-year-old-group (HR-genotypes) (Table 2).

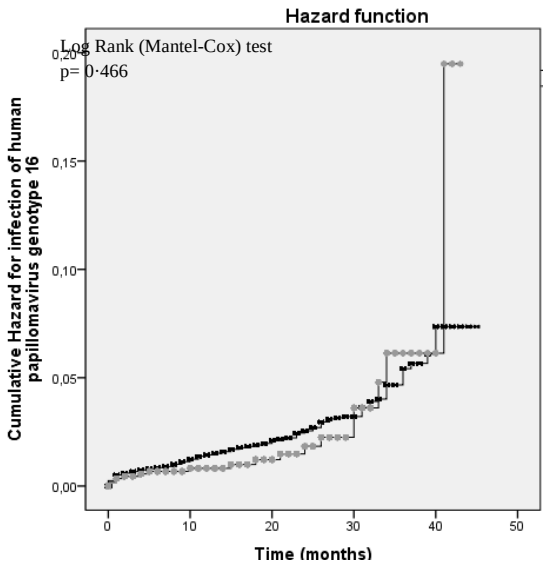
Moreover, the distribution of HPV infection, by age-group, is different between women with or without diabetes. In patients with diabetes, the CIR of HPV infection by genotype 16 (per 1000 person-years) was highest in women in the 75–79 year-group, but in subjects without diabetes this incidence was the highest in younger women than 25 years old. In contrast, the highest incidence of infection by genotype 18 was in the 75–79-year-old-group for women without diabetes, and in patients with diabetes it was in the 20–24 year- group. Additionally, the CIR of infection by genotype of HR was the highest in age-groups between 15 and 29 years old for subjects without diabetes. But in women with diabetes this incidence was the highest in subjects in the next age-groups: 15–19 years old, 25–29 years, 30–34 years old, and 40–44 years old (Table 2). Kaplan-Meier hazard curves are present in Fig. 2.

The crude hazard ratio of infection by all genotypes of HPV was lower in women with diabetes compared to their counterparts without diabetes (showed not association) (Table 3), however, the crude hazard ratio of infection by HPV-18 genotype was higher in women with diabetes and ages between 20-24 years old (HR= 36.611; 95% CI 4.009-334.303, p= 0.001), and 40-44 years old (OR= 3.954; 95% CI 1.112-14.060, p= 0.034, HR= 3.947; 95% CI 1.124-13.857, p= 0.032) compared to their counterparts without diabetes.

a)



b)



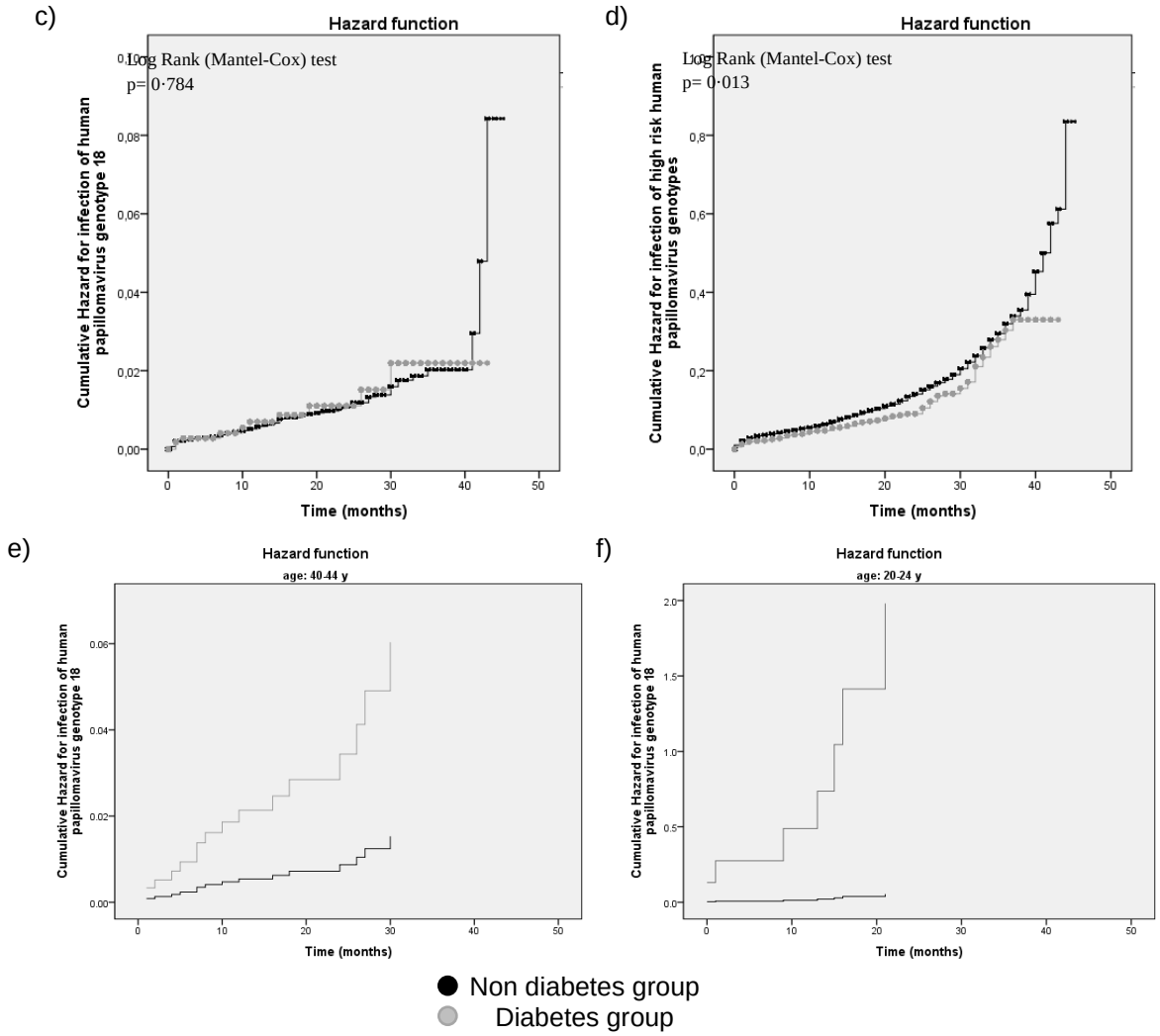


Fig. 2. Kaplan-Meier Hazard curve

a) Infection with any human papillomavirus genotypes. b) Infection with human papillomavirus genotype 16. c) Infection with human papillomavirus genotype 18. d) Infection with high-risk human papillomavirus genotypes. e) Infection with human papillomavirus genotype 18 and patients between 40 to 44 years old. f) Infection with human papillomavirus genotype 18 and patients between 20 to 24 years old

Table 3. Cox regression analyses of the association among glucose plasma concentration, and type 2 diabetes with human papillomavirus infection, by genotype

Any HPV genotype	HR (95% CI)	P value
Glucose	0.998 (0.995-1.000)	NS
Diabetes	0.975 (0.748-1.272)	NS
HPV-16		
Glucose	0.999 (0.993-1.006)	NS
Diabetes	0.841 (0.423-1.673)	NS
HPV-18		
Glucose	0.998 (0.990-1.007)	NS
Diabetes	1.269 (0.517-3.114)	NS
HPV-HR		
Glucose	0.998 (0.995-1.000)	NS
Diabetes	0.994 (0.746-1.325)	NS

CI: confidence interval, HR: hazard ratio. CI and p value, for prevalence, were calculated using logistic regression model. CI and p value for HR were calculated using Cox proportional-hazards regression analysis

Table 4. Background of Pap smear and PCR test, of study population

Variables	Total population N=13234 N (%; 95% CI)	Group with diabetes n= 1215 n (%; 95% CI)	Group without diabetes n= 12019 n (%; 95% CI)	P Value
Period of time	Last Pap Smear			
First time	1487 (11·2; 10·7-11·8)	117 (9·6; 8·0-11·4)	1370 (11·4 (10·8-12·0)	NS
1 year or less	5811 (43·9; 43·0-44·7)	524 (43·1; 40·2-45·8)	5287 (44·0; 43·1-44·9)	NS
2-3 years	3694 (27·9; 27·1-28·7)	342 (28·1; 25·8-30·8)	3352 (27·9; 27·0-28·7)	NS
3 years or more	1512 (11·4; 10·9-12·0)	164 (13·5; 11·6-15·7)	1348 (11·2; 10·6-11·8)	0·019
Unknown	730 (5·5; 5·1-5·9)	68 (5·6; 4·3-6·9)	662 (5·5; 5·1-5·9)	NS
Previous result	Last PCR test			
HPV positive samples	121 (0·9; 0·8-1·1)	8 (0·7; 0·2-1·2)	113 (0·9; 0·8-1·1)	NS

PP: Positive previous· NP: Negative previous·
p Value was calculated by Chi square test and Fisher Exact test·

Furthermore, the prevalence of previous HPV infection was similar in both groups (Table 4). Nevertheless, women with diabetes undergo Papanicolaou smear procedure less frequently than women without diabetes (Table 4).

4. DISCUSSION

This study provides evidence of the burden of HPV infection in women with diabetes. According to Bruni et al [7] the estimated global HPV prevalence in women with normal cytology was 11.7%, similar to our findings (11.3%). However, this prevalence is lower compared with prevalence observed by Sub-Saharan Africa (24.0%), Eastern Europe (21.4%), and Latin America (16.1%) [7].

Additionally, our findings confirm that HPV infection is more common in women younger than 30 years of age, but compared with women from other America regions, women with diabetes showed different age-specific HPV prevalence patterns, with a peak in women under 25 years of age, and a second peak in women in the 75–79-year-old-group. In contrast, women from several regions in the Americas showed a peak in HPV prevalence in women aged 45 years old and older [8]. Even more, the HPV prevalence in women with diabetes (9.0%) is lower compared to HPV prevalence observed in women from several regions of America (Central America: 20.4%, South America: 12.3%, and Northern America: 11.3%), several regions from Africa (Eastern Africa: 31.6%, Northern Africa: 21.5%, Southern Africa: 15.5%, and Western Africa: 17.0), Russia (29.1%) and women from China and South Korea (13.6%) [7-8]. However, it is significantly higher compared to women from several regions of Southern (Greece, Italy, and Spain: 6.8%), and Western Europe (Belgium, France, Germany, and Netherlands: 8.4%), from Southeastern Asia (Philippines, Thailand, and Vietnam: 6.2%), women from India (7.5%) [8], and from Morocco-Africa (4.2%) [7]; but it was similarly compared to women from Northern Europe (Denmark, Sweden, and United Kingdom: 7.9%), from Japan and Taiwan (7.0%), and from several countries of Africa (Algeria: 10.5%; Egypt: 10.3%; Tunisia: 14.4%, Gambia: 11.5%, and Senegal: 13.9%) [8]. In Mexico, the prevalence of HPV infection is different among geographic regions. The HPV prevalence observed in women with diabetes of our study population, is significantly lower compared to the HPV prevalence in women from Acapulco (35.5%), Morelos (12.5%) [9], Guadalajara (33.9%), and from the southwest Pacific coast of Mexico (43.6%; Acapulco, Guerrero, and Michoacán) [10], but it is higher regarding to Durango (4.1%), and similar to women from Mexico City (from 9.1 to 11.9) [7,11].

Additionally, incidence rates were significantly higher among women with diabetes compared to women without diabetes in several age- groups. The incidences of any HPV per 1000 person-years ranged from 60.39 to 833.33 for women with diabetes versus 40.43 to 274.90 for patients without diabetes. Similarly, the incidences of HR-, 16- and 18-HPV per 1000 person-years ranged from 38.70 to 833.33, 7.62 to 113.64, and 7.62 to 833.33 versus 40.66 to 238.52, 7.91 to 52.5, and 1.86 to 40.45 in women with and without diabetes, respectively. The cumulative incidence of any HPV infection, and for HR-HPV infection by 3.6 years was substantially higher in women under 25 years old (with diabetes) than in women

in the same age-group without diabetes (833.33/1000 person-years vs. 266.26/1000 person-years, and 416.67/1000 person-years vs. 231.22/1000 person-years, respectively). The incidence rate in women with diabetes between 19 and 34 years old was higher compared to those young women aged 18-35 from Southern Arizona (145.01/1000 person-year vs. 29.4/1000 person-year, respectively) [12], and from Arizona (35.3/100 person-years) [13]. However, the available data suggest a high incidence of any and HR-HPV infections in women with diabetes but these incidences could have not compared to the incidence of other populations. These findings implicate different screening programs and strategies for timely detection of HPV infection in younger women and in older women with diabetes. Even more, our findings show a different distribution of HPV genotypes according to age, suggesting that screening strategies could have different impact and magnitude in relation to age. However, our results, in people with diabetes, are different to the well-established paradigm that the infection prevalence of human papillomavirus (HPV-16 and/or -18) decreases with increasing age. According to previous reports this prevalence has a peak in middle-aged women (35-50 years old) from different geographical regions [14], but we observed two peaks in women under 30 years old, and older than 50 years old. These findings are similar to the results obtained in women from North of Mexico City [15]. Moreover, the present study also provides evidence related to the association between metabolic diseases and the risk of HPV infection in young Mexican adult women [6,16-17]. In addition, t2DM increases the risk of HPV-18 genotype infection in young adult women with a probability of 79.8%. However, the hazard ratio for women aged 20 to 24 is very large, suggesting that more studies should be conducted in this population group. In consequence, this study contributes to the knowledge, especially in countries where HPV is an important cause of sexual infection and the prevalence of t2DM is increasing. Consequently, we recommend the implementation of routine screening of HPV infection in patients with diabetes.

5. CONCLUSION

This study establishes evidence that diabetes is a factor associated to an increase in the risk of HPV-18 genotype infection only in young women (age range of 40 to 44 years).

DECLARATION

This study was conducted in accordance to Good Clinical Practice of our Laws and the Helsinki declaration. For this research, experiments in humans and animals have not been conducted, and patient data does not appear.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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