Original Article

Human papillomavirus prevalence and dynamics

Insights from a 5-year population-based study in Jeddah, Kingdom of Saudi Arabia

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ABSTRACT

الأهداف: تقدير معدل الانتشار المصلي لفيروس الورم الحليمي البشري (HPV) بين النساء السعوديات وتقييم الديناميات المصلية لـ HPV على مدى خمس سنوات.

المنهجية: أجريت دراسة شاملة مبنية على السكان، شملت 5360 امرأة متزوجة تتراوح أعمارهن بين 30–65 عامًا من جدة، المملكة العربية السعودية ما بين 2013–2018م. تم تسجيل المشاركات من خلال برنامج فحص معين واستخدام طريقة HPV (hr HC2) للفحص. النساء اللاتي ظهرت نتائجهن إيجابية لـ HPV خضعن لمتابعة لمدة عام واحد لتقدير معدل التحول إلى السلبية المصلية، بينما تم متابعة اللاتي ظهرت نتائجهن سلبية بعد خمس سنوات لتحليل التحول الإيجابي المصلي. تم تحليل العوامل الاجتماعية الديموغرافية والسريرية المرتبطة بالإيجابية المصلية والسلبية المصلية.

النتائج: بلغ متوسط العمر ومدة الزواج على التوالي 44.3 و22.6 عامًا، وكان متوسط عدد الأطفال هو 4. بلغ معدل الانتشار المصلي الأساسي 4.7%. بعد عام من الفحص، بلغ معدل التحول إلى السلبية المصلية 84.3%. بعد مرور خمس سنوات، بلغ معدل الإيجابية المصلية بين النساء اللاتي كانت نتائجهن سلبية في البداية 0.2%، مما أدى إلى معدل انتشار مصلي إجمالي قدره 5%. بناء على هذا، قدر معدل الحدوث لـ HPV بـ 47 لكل 100،000 شخص في السنة. برز عدد الأطفال كعامل مستقل وحيد للإيجابية المصلية، مع وجود تأثير واقي بنسبة احتمالات (OR) قدرها 0.93 (مجال الثقة 95%: 0.8 – 0.99).

الخلاصة: يبقى معدل الانتشار المصلي ومعدل الحدوث المصلي لفيروس HPV بين النساء السعوديات منخفضا بشكل ملحوظ، مما يشير إلى تقدم التفشي المحلي ببطء. تسلط الدراسة الضوء على عامل جيلي، مما يبرز الحاجة لمزيد من البحث لتوقي التحديات وتصميم استراتيجيات الوقاية والفحص في المملكة العربية السعودية.

Objectives: To estimate the prevalence and dynamics of human papillomavirus (HPV) infection, over a 5-year period, among Saudi women.

Methods: A 2-phase, population-based study combining cross-sectional and cohort designs was carried out with 5360 ever-married women aged 30–65 from Jeddah, Saudi Arabia, between 2013 and 2018. Participants were enrolled in a designated screening program and screened using the hybrid capture 2 HPV test. Women testing positive for HPV were followed up after one year to estimate the HPV clearance rate, while those testing negative had a follow-up after 5 years to assess new HPV infections. Factors associated with HPV positivity and clearance, including sociodemographic and clinical aspects, were analyzed.

Results: Participant's mean age was 44.3 and the average marriage duration was 22.6 years. The initial HPV prevalence was 4.7%. After one year, the HPV clearance rate among initially positive women was 84.3%. The rate of new HPV infections among initially negative women after 5 years was 0.2%, resulting in a cumulative HPV prevalence of 5% over the study period. The incidence rate was estimated at 47 per 100,000 person-years. Parity was the only independent factor inversely associated with HPV positivity, with an odds ratio of 0.93 (95% confidence interval: 0.8 – 0.99).

Conclusion: The prevalence of HPV in Saudi women was relatively low, suggesting a low transmission rate of HPV. This finding indicates the need for continuous monitoring and tailored prevention strategies.

Keywords: HPV prevalence, HPV dynamics, HPV clearance, Saudi Arabia

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Human papillomavirus (HPV) is known for its potential to induce tumorigenesis through its oncoproteins E6 and E7.[1] It represents the primary cause of cervical cancer, accounting for the fourth most frequent female cancer worldwide. In 2020, approximately 604,000 new cases and 342,000 deaths from cervical cancer were reported worldwide.[2]

The highest incidences were in South-central Asia and Eastern Asia, with economically lower-middle-income countries also significantly affected.[2] Human papillomavirus is a leading cause of infection-induced cancers, second only to *Helicobacter pylori*, and is associated with a broad spectrum of malignancies, including the majority of cervical and anal cancers, as well as substantial proportions of vaginal, vulvar, penile, and oropharyngeal cancers.[3,4]

In Western societies, the likelihood of contracting genital HPV infection is higher among sexually active women with new or multiple sexual partners or those with non-monogamous partners.[5]

In Saudi Arabia, hospital-based studies have shown HPV prevalence ranging from 9.8% to 43%, predominantly involving high-risk (HR) strains like genotypes 16, 18, and 45, which are strongly linked to cervical cancers.[6,7] This indicates a significant risk of HPV-related cancers among Saudi women. Local data suggest that approximately 55 women die annually from HPV-related cancers, which places the 10.3 million Saudi women of reproductive age at risk of such malignancies.[8,9]

Despite the growing incidence and mortality from cervical cancers in Saudi Arabia, owing to population growth, the true extent of HPV infection is likely underestimated due to inadequate screening practices.[10] Effective HPV vaccination and screening programs have significantly reduced cervical cancer cases globally.[11] Conventional screening methods like the Papanicolaou (Pap) smear enable early detection of precancerous lesions and offer a chance for conservative, curative treatment methods. Additionally, HPV DNA testing plays a crucial role in identifying HR genotypes, necessitating rigorous follow-up.[12]

In Saudi Arabia, expert panels recommend screening for cervical intraepithelial neoplasia (CIN) using Pap smear and colposcopy, or HPV DNA testing followed by colposcopy.[10] Unfortunately, more than 7 out of 10 cervical cancer cases in Saudi women are detected at an advanced stage due to the lack of comprehensive screening programs.[13] In the absence of national data, identifying HPV infection trends in Saudi Arabia is essential.[14,15] The present study, therefore, aims at estimating the prevalence of HPV infection among Saudi women and determining its dynamics over a 5-year period, utilizing the Hybrid Capture 2 (HC2) HPV DNA test for cervical samples. The study also analyzes factors associated with HPV positivity and clearance.

Methods. This study utilized a 2-phase design combining cross-sectional and cohort methodologies, focusing on non-hospital-based women, as part of a pilot nationwide cervical cancer screening program. The study was ethically approved by the Biomedical Ethics Research Committee (Reference No. 694-12). The target population included women aged 30 to 65 who had been married for over 3 years, excluding those with prior cervical dysplasia, cervical cancer, or a history of hysterectomy. The study faced challenges in identifying sexually active women within the defined age range, leading to the inclusion of all eligible women who participated in screening campaigns and consented to the research. We obtained verbal consent from all participants, after explaining the HPV test and collecting personal and medical history. This consent included permission for using clinical and screening data for research purposes, with assurance of the right to refuse participation without affecting care, adhering to ethical principles.

Human papillomavirus testing was carried out using the HC2 test for HR HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)". These analyses were carried out at the virology department of the center, with strict quality assurance maintained.

Participant recruitment for the large-scale HPV screening program involved various channels, including social media, primary health care clinics, collaborations with the Ministries of Health and Education, and female university employees.

For HPV testing, cervical swabs were collected using the HC2 method. The initial phase of sample collection was carried out at King Abdulaziz University Hospital's screening unit, and the second phase involved primary health care centers.

Follow-up procedures varied based on initial test results. Participants with a negative HPV result were scheduled for a repeat test after 5 years. Those who tested positive underwent reflex cytology and colposcopy, with a cervical biopsy if required, following American

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Cancer Society guidelines for management of CIN2+ by a gynecology oncology team.

Cervical biopsies were evaluated histopathologically to identify the extent of abnormal cellular changes, classifying samples as CIN 1, CIN 2, or CIN 3 based on dysplasia severity.

Monitoring in the study was focused on 2 key aspects: HPV clearance, defined as a change from HPV positive to HPV negative status, and the acquisition of a new HPV infection, indicated by a shift from HPV negative to HPV positive status. Women who initially tested positive were scheduled for a retest one year later, provided their subsequent Pap smear and colposcopy results were negative. Conversely, participants who initially tested negative for HPV were scheduled for a retest after a 5-year interval.

Initial data were systematically recorded in a comprehensive database equipped with a recall system. Test results were diligently tracked, and participants were contacted by the program team for follow-up. A structured Excel sheet was used to collect the following data: i) sociodemographic and obstetrical data, including age, marital status, education, age at marriage, marriage duration, and parity; ii) medical data, such as comorbidities, smoking status, HPV vaccination status, and family history of gynecological or other cancers; iii) baseline screening results, indicating HPV DNA test status; iv) one-year follow-up results for initially HPV-positive participants; and 5) 5-year follow-up screening results for initially HPV-negative participants.

This study evaluated 4 primary outcomes: a) Baseline HPV prevalence: Calculated at the study's initial phase, representing the fraction of participants who tested HPV-positive during the initial screening campaign. b) HPV clearance: Represented by the percentage of women who transitioned from an HPV-positive status at initial screening to an HPV-negative status one year later. c) New HPV infections: The percentage of women who shifted from an HPV-negative status during the initial screening to an HPV-positive status after 5 years. d) Cumulative HPV incidence: The percentage of participants who had a positive HPV testing at any point during the total follow-up period, relative to all participants.

Statistical analysis. Statistics were conducted in SPSS, version 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics used frequencies and percentages for categorical variables and mean ± standard deviation (SD) or median (75th percentile [P75]) for continuous variables. Factors associated with cumulative HPV positivity and clearance were analyzed using the independent t-test or the Mann-Whitney U test for continuous variable, and chi-square test or Fisher's exact test for categorical variables, as applicable. Univariate and multivariate logistic regression was used to analyze the independent factors influencing cumulative HPV positivity and clearance. The null hypothesis was rejected for a p-value of <0.05.

Results. The first screening campaign totalized 5360 women, from 2013 to 2018; their mean age was 44.3 years (SD=8.3). Of these, 92.5% were married, with an average marriage duration of 22.6 years (SD=10.0 years), and a median parity of 4 (P75=6). The majority had completed high school (57.8%) or university education (30.1%).

Medical history. Approximately 28.1% of the participants reported at least one comorbidity. The most common were hypertension (14%), diabetes mellitus (11.2%), and thyroid dysfunction (7.1%). Only 4 participants (0.1%) were vaccinated against HPV. A family history of malignancy was reported by 17.2% of women, with 9.1% reporting a history of gynecological cancers (Table 1).

Human papillomavirus prevalence and infection dynamics. At baseline, 254 of the 5360 participants tested positive for HPV (baseline HPV prevalence=4.7%; 95% confidence interval (CI): 4.2–5.3%). Among these, 16 (6.3%) individuals had CIN2+ lesions, representing 0.3% of the total population (95% CI: 0.2–0.5%) Figure 1.

After one year of follow-up, 214 of the 254 initially HPV-positive individuals tested negative, indicating an HPV clearance rate of 84.3%. After 5 years, 12 out of the 5106 initially HPV-negative individuals acquired a new HPV infection (new HPV infection rate=0.2% [95% CI: 0.1-0.4%]), resulting in an incidence rate of 47 per 100,000 person-years.

The cumulative HPV incidence over the 5-year follow-up period was 5% (95% CI: 4.4-5.6%), representing 266 out of 5360 participants.

Factors associated with cumulative HPV positivity. Compared to HPV-negative women, those who tested HPV-positive were approximately 2 years younger and had lower parity; both results had a p-value of 0.001. HPV positivity rates were significantly higher among highly educated women (p=0.037), but paradoxically lower among those with multiple comorbidities (p=0.008), diabetes (p=0.006), or hypertension (p=0.040). On the other hand, HPV status showed no association with oral contraception use (p=0.399) or family history of malignancy (p=0.968) (Table 2).

Predictors of cumulative HPV positivity. In univariate regression models, each additional year of age accounted

Table 1 - Participant's demographic characteristics (N=5360).

Parameter	n	%
Age		
Years	44.31±8.29	
Age at marriage		
Years	21.70±5.51	
Marriage duration		
Years	22.61±10.01	
Parameter		
Level	Median	P75
Parity		
N (range: 0-8)	4	6
Marital status		
Married	4956	92.5
Divorced	250	4.7
Widowed	154	2.9
Education		
Illiterate	286	5.3
Primary	364	6.8
High school	3096	57.8
University	1614	30.1
*Number of comorbidities**		
0	3856	71.9
1	1018	19.0
2	386	7.2
>3	100	1.9
Smoking		
No	4928	91.9
Yes	432	8.1
Oral contraceptive use		
No	3672	68.5
Yes	1688	31.5
Human papillomavirus vaccination		
No	5356	99.1
Yes	4	0.1
Family history of cancer		
None	4438	82.8
Yes	992	17.2
Gynecological	487	9.1
Non-gynecological	430	8.0
Not specified	5	0.1

*hypertension 14%, diabetes mellitus 11.2%, thyroid 7.1%

for a 2% decrease in the likelihood of HPV positivity (odd ratio [OR]=0.98; 95% CI: 0.96-0.99), and each additional childbirth accounted for a 9% decrease (OR=0.91; 95% CI: 0.86-0.96). Higher education increased the likelihood of HPV positivity (OR=1.7; 95% CI: 1.1-2.8), while having multiple comorbidities (OR=0.4; 95% CI: 0.2-0.7), diabetes (OR=0.5; 95% CI: 0.3-0.8), or hypertension (OR=0.65; 95% CI: 0.4-0.98) decreased it. In multivariate analysis, only parity remained independently associated with HPV positivity, showing an inverse relationship (OR=0.93; 95% CI: 0.8 – 0.99) (Table 3).

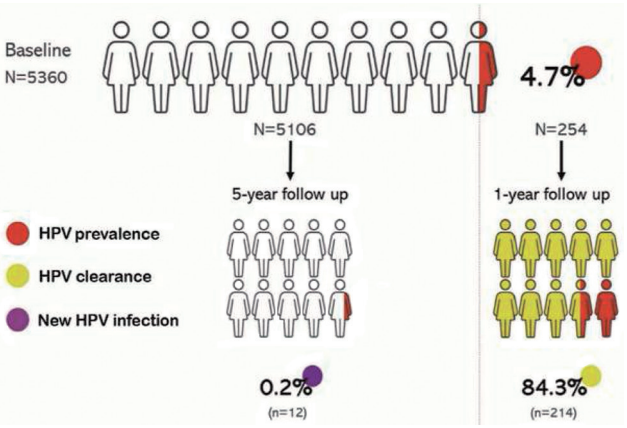

Figure 1 - Overview of human papillomavirus (HPV) prevalence and clearance rates over a 5-year period.

Factors and predictors of HPV clearance. Human papillomavirus clearance was associated with younger age (mean age=41.9 [SD=8.25] vs 45.85 [10.1] years for those without clearance, p=0.008). The rate of HPV clearance was lower in divorced women (60%) compared with married (86%), and widowed women (100%) (p=0.005)(Table 4).

Each one-year increase in age decreased the likelihood of HPV clearance by 5% (OR=0.95; 95% CI: 0.92-0.99), while being divorced decreased it by 76% (OR=0.24; 95% CI: 0.09-0.63). Both age and divorced status were independently associated with HPV clearance in an inverse relationship (Table 5).

Discussion. The analysis and monitoring of HPV prevalence in a population are vital for informing preventive strategies and prioritizing care actions. This 5-year population-based study revealed a low HPV prevalence of 4.7% among Saudi women, increasing slightly to 5% after a 5-year follow-up. We estimated the incidence rate of new HPV infections at 47 per 100,000 person-years. The likelihood of HPV positivity decreased with older age and higher parity, and in cases with significant medical comorbidities, while it was higher among highly educated women. Notably, parity was the only factor independently associated with HPV positivity, showing an inverse relationship. A high rate of HPV clearance was observed one year after initial screening, with 84.3% of initially HPV-positive individuals testing negative. Older age and divorced status were negative predictors of HPV clearance. Additionally, the assessment of cervical cancer risk indicated that HPV positivity was associated with a 6.3% risk of CIN2+. By considering HPV-negative women as having Pap tests indicative of less than CIN2

Table 2 - Factors associated with cumulative human papillomavirus positivity.

Factors	Serological status				*P*-value
	Negative		Positive		
	n	%	n	%	
Age					
Years	44.39±8.25		42.73±8.75		0.001*[t]
Age at marriage					
Years	21.69±5.48		21.94±5.97		0.468[t]
Marriage duration					
Years	22.71±9.96		20.79±10.69		0.002*[t]
Parameter					
Level	Median	P75	Median	P75	
Parity					
N	4	6	4	5	0.001*[M]
Marital status					
Married	4716	95.2	240	4.8	
Divorced	230	92.0	20	8.0	
Widowed	148	96.1	6	3.9	0.067
Education					
Illiterate	276	96.5	10	3.5	
Primary	354	97.3	10	2.7	
High school	2946	95.2	150	4.8	
University	1518	94.1	96	5.9	0.037*
Number of comorbidities					
0	3652	94.7	204	5.3	
1	966	94.9	52	5.1	
2	376	97.4	10	2.6	
3+	100	100.0	0	0.0	0.013*
Smoking					
No	4688	95.1	240	4.9	
Yes	406	94.0	26	6.0	0.392
Diabetes mellitus					
No	4510	94.7	250	5.3	
Yes	584	97.3	16	2.7	0.006*
Hypertension					
No	4368	94.8	240	5.2	
Yes	726	96.5	26	3.5	0.040*
Thyroid disease					
No	4732	95.0	250	5.0	
Yes	362	95.8	16	4.2	0.498
Oral contraceptive use					
No	3496	95.2	176	4.8	
Yes	1598	94.7	90	5.3	0.399
HPV vaccination					
No	5090	95.0	266	5.0	
Yes	4	100.0	0	0.0	1.000[F]
Family history of cancer					
No	4218	95.0	220	5.0	
Yes	876	95.0	46	5.0	0.968
Family history of cancer					
No	4218	95.0	220	5.0	
Gynecological	464	95.3	23	4.7	
Non-gynecological	412	94.7	23	5.3	0.925

Test used: t independent t-test, M: Mann-Whitney U test, F: Fisher's exact test, otherwise, Chi square test was used, * statistical significance

Table 3 - Predictors of cumulative human papillomavirus positivity.

	Univariate model				Multivariate model			
Predictor	**OR**	**95%CI**		***P*-value**	**OR**	**95%CI**		***P*-value**
Age	0.98	0.96	0.99	0.001*	0.99	0.97	1.00	0.137
Marriage duration	1.01	0.99	1.03	0.467	-	-	-	-
Parity	0.91	0.86	0.96	<0.001*	0.93	0.88	0.99	0.020*
Education								
Illiterate	Ref			0.040*	-	-	-	-
Primary	0.78	0.32	1.90	0.584	-	-	-	-
High school	1.41	0.73	2.70	0.306	-	-	-	-
University	1.75	0.90	3.39	0.100	-	-	-	-
Number of comorbidities								
0	Ref			0.012*	Ref			0.201
1	0.96	0.70	1.32	0.817	1.17	0.78	1.75	0.453
2+	0.38	0.20	0.71	0.003*	0.62	0.25	1.52	0.295
Diabetes mellitus								
No	Ref				Ref			
Yes	0.49	0.30	0.83	0.007*	0.73	0.38	1.38	0.328
Hypertension								
No	Ref				Ref			
Yes	0.65	0.43	0.98	0.042*	0.92	0.53	1.61	0.772

*Statistically significant result ($p<0.05$). OR: Odds ratio, CI: confidence interval, Ref (reference): category used a reference to calculate OR

stage, the overall prevalence of CIN2+ among the total participants was estimated at 0.3%.

Human papillomavirus prevalence and incidence. Over the 5-year follow-up period in this study, predominantly among HPV-unvaccinated women (only 4 were vaccinated), the prevalence of HPV positivity rose from 4.7% to 5%, resulting in a relatively low incidence rate of 47 per 100,000 person-years. This finding is comparable to a low HPV prevalence of 2.8% reported by Mousa et al[8] among women attending a gynecology clinic in Jeddah, Saudi Arabia, in 2017–2018. These local HPV prevalence rates are notably lower than those found in other regions such as the USA (40.5%).[16] This lower prevalence and incidence among the Saudi population is likely attributed to protective sexual behaviors, with most Saudi women having a single lifetime partner and engagement in other risky sexual behaviors being rare in conservative Muslim societies. Additionally, male circumcision, a common practice in Muslim populations, has been liked to a lower risk of HPV infection in monogamous women.[17]

Prevalence and risk of CIN2 lesions. We observed a 6.3% risk of CIN2+ lesions among HPV-positive women, resulting in an overall prevalence of CIN2+ lesions estimated at 0.3% in the cohort. Despite potential discrepancies between HPV DNA test results and CIN profiles, these findings support the utility of integrating HPV DNA testing with colposcopy and biopsy in screening strategies. Persistently positive HPV DNA test results could be used alongside other risk factors, such as older age, smoking, oral contraceptive use, and personal history of Chlamydia infection, to evaluate the risk of cervical carcinoma.[18] The low rates of CIN2+ lesions reflect the low prevalence of HPV infections in the Saudi population. However, this should not diminish the importance of ongoing prevention and screening efforts for HR HPV genotypes and their associated morbidity.

Human papillomavirus clearance rate. Our findings indicated that a majority of initially HPV-positive women (84.3%) tested HPV-negative after one year of follow-up. This aligns with previous research showing a high rate of natural HPV clearance.[19,20] This suggests that a positive HPV DNA in the context of Saudi Arabia could be considered a transient finding, especially in cases with negative dysplasia results, and would warrant simple monitoring. This underscores that monitoring the dynamics of HPV DNA test results is more reliable than a one-time HPV DNA test result in evaluating infection status and its potential risks.

Factors influencing HPV positivity. In our study, parity emerged as the only independent factor inversely associated with HPV positivity. While parity is recognized as a risk factor for cervix squamous-cell carcinoma in HPV-positive women with persistent infection,v its impact on the acquisition of HPV may differ.[21] We observed that participants with fewer childbirths had significantly higher rates of HPV

Table 4 - Factors associated with HPV clearance (N=254).

Factor	Seronegativation				*P*-value
	No		Yes		
	n	%	n	%	
Age	45.85	10.13	41.91	8.25	0.008*[t]
Age at marriage	22.95	7.28	21.78	5.62	0.249[t]
Marriage duration	22.90	11.46	20.13	10.43	0.130[t]
Parameter	Median	P75	Median	P75	p-value
Parity	4	5.75	3	5	0.639[M]
Marital status					
Married	32	14.0	196	86.0	
Divorced	8	40.0	12	60.0	0.005*
Widowed	0	0.0	6	100.0	
Education					
Illiterate	4	40.0	6	60.0	
Primary	0	0.0	8	100.0	0.100
High school	24	16.2	124	83.8	
University	12	13.6	76	86.4	
Number of comorbidities					
0	26	13.4	168	86.6	
1	12	24.0	38	76.0	0.173
2	2	20.0	8	80.0	
Smoking					
No	36	15.7	194	84.3	1.000[F]
Yes	4	16.7	20	83.3	
Diabetes mellitus					
No	40	16.8	198	83.2	
Yes	0	0.0	16	100.0	0.084[F]
Hypertension					
No	34	14.8	196	85.2	
Yes	6	25.0	18	75.0	0.191
Thyroid disease					
No	36	15.1	202	84.9	
Yes	4	25.0	12	75.0	0.291F
Oral contraceptive use					
No	22	13.3	144	86.7	
Yes	18	20.5	70	79.5	0.134
Family history of cancer					
None	36	17.1	174	82.9	
Yes	4	9.1	40	90.9	0.255[F]

Test used: t independent t-test, M: Mann-Whitney U test, F: Fisher's exact test, otherwise, Chi square test was used, * statistical significance

positivity. The protective impact of parity: compared to nulliparous women, who had several pregnancies were less likely to contract numerous HR HPV strains. This may be explained by the fact that women who have had several pregnancies tend to conduct more virtuous and conservative lives, which may minimize their exposure to STDs, such as HPV.

The use of oral contraceptive pills (OCP) constitutes a major factor for HPV acquisition in women with no previous infection.[22] The mechanisms through which OCP may promote HPV infection include increased cervical ectropion occurrence, hormone-mediated stimulation of HPV DNA transcription, and alteration in host immune response.

Conversely, univariate analysis revealed an inverse relationship between HPV positivity and age. This is consistent with existing data showing that younger age increases the risk of HPV infections among sexually active women, while older age acts as a protective factor.[23] Younger women often have limited knowledge and experience regarding sexual hygiene and safety methods, such as condom use, making them more vulnerable to STDs. Additionally, younger generations may have less stable marital relationships, increasing the likelihood of changing partners, which increases the risk of HPV infection.[23]

Impact of comorbidities on HPV positivity. Interestingly, our findings showed that women with comorbidities had a reduced risk of HPV positivity compared to their healthy counterparts. This might be explained by a decrease in sexual desire and frequency of intercourse associated with certain comorbidities, consequently reducing the likelihood of HPV infection.[24] For instance, sexual dysfunction is reported in a significant percentage of women with diabetes mellitus, impacting sexual desire and activity.[25] Similarly, hypertension in women can lead to various sexual difficulties, including a decrease in the frequency of sexual contact.[26] Since higher sexual activity is a recognized risk factor for HPV infection, a reduction in sexual encounters due to comorbidities might negatively affect the chances of acquiring HPV.[24-26]

Educational level and HPV positivity. The present study also found a higher rate of HPV positivity among highly educated women, although this association was not confirmed in multivariate analysis. This could be confounded by factors such as generational trends towards higher education or a greater willingness among educated women to participate in HPV screening. Higher education levels have been associated with more frequent uptake of preventive measures like screening and HPV vaccination.[27] However, this poses a potential selection bias that should be considered in screening programs.

Factors influencing HPV clearance. There was an observed inverse relationship between age and HPV clearance. With each additional year of age, the likelihood of HPV clearance decreased by 5%, indicating that older women are more prone to experience persistent HPV infections. This could be explained by senescence of the immune system, which may diminish the body's effectiveness in eradicating viral infections, including HPV.[28] Additionally, divorced status emerged as

Table 5 - Predictors of human papillomavirus clearance.

	Univariate Model				Multivariate Model			
Predictor	**OR**	**95%CI**		***P*-value**	**OR**	**95% CI**		***P*-value**
Age	0.95	0.92	0.99	0.009*	0.95	0.92	0.99	0.012*
Divorced status								
No	Ref				Ref			
Yes	0.24	0.09	0.63	0.004*	0.24	0.09	0.65	0.005*

*Statistically significant result (p<0.05). OR: Odds ratio, CI: confidence interval, Ref: category used a reference to calculate OR

another negative predictor for HPV clearance. Divorce, potentially indicative of an unstable sexual life, has been associated to an increased risk of STDs. Previous studies have also shown that divorced or separated individuals face a higher risk of infectious diseases, with this risk being more pronounced in women.[29]

In conclusion, HPV prevalence in Saudi women is notably low, with an incidence rate estimated at 47 per 100,000 person-years, indicating a low transmission rate of HPV. Young women, in particular, appear more susceptible to acquiring HPV, suggesting a generational trend that warrants further investigation. This underlines the importance of targeted education to reduce the risk of STDs and promote healthier sexual practices.

Regarding the dynamics of HPV infection, the majority of cases show favorable outcomes, a factor that gynecologists should consider, particularly in cases of isolated positive HPV tests. Special attention is needed for monitoring older and divorced women with positive HPV results, as they have a higher likelihood of persistent infection and, consequently, an increased risk of developing squamous cell carcinoma.

The inferred generational effect from this study calls for more comprehensive research to better understand future challenges. This knowledge is crucial for developing adaptive prevention and screening strategies tailored to the needs of the population in Saudi Arabia

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References

1. Pal A, Kundu R. Human papillomavirus E6 and E7: the cervical cancer hallmarks and targets for therapy. ***Front Microbiol*** 2020; 10: 3116.
2. World Health Organization. Cervical cancer (Updated 2023; Cited date 2023 Nov 17). Available from: https://www.who.int/news-room/fact-sheets/detail/cervical-cancer
3. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. ***Lancet Glob Health*** 2020; 8: e180-e190.
4. Centers for Disease Control and Prevention. Cancers associated with human papillomavirus. (Updated 2023; Cited date 2023 Feb 04). Available from: https://www.cdc.gov/cancer/hpv/basic_info/cancers.htm
5. Huang J, Deng Y, Boakye D, Tin MS, Lok V, Zang L, et al. Global distribution, risk factors, and recent trends for cervical cancer: A worldwide country-level analysis. ***Gynecol Oncol*** 2022; 164: 85-92.
6. AlObaid A, Al-Badawi IA, Al-Kadri H, Gopala K, Kandeil W, Quint W, et al. Human papillomavirus prevalence and type distribution among women attending routine gynecological examinations in Saudi Arabia. ***BMC Infect Dis*** 2014; 14: 643.
7. Turki R, Sait K, Anfinan N, Sohrab SS, Abuzenadah AM. Prevalence of human papillomavirus in women from Saudi Arabia. ***Asian Pac J Cancer Prev*** 2013; 14: 3177-3181.
8. Mousa M, Al-Amri SS, Degnah AA, Tolah AM, Abduljabbar HH, Oraif AM, et al. Prevalence of human papillomavirus in Jeddah, Saudi Arabia. ***Ann Saudi Med*** 2019; 39: 403-409.
9. ICO/IARC Information Centre on HPV and Cancer. Saudi Arabia - Human papillomavirus and related cancers, fact sheet 2021. [Updated 2023 Mar 10; Cited 2023 Aug 26]. Available at: https://hpvcentre.net/statistics/reports/SAU_FS.pdf
10. Al-Mandeel HM, Sagr E, Sait K, Latifah HM, Al-Obaid A, Al-Badawi IA, et al. Clinical practice guidelines on the screening and treatment of precancerous lesions for cervical cancer prevention in Saudi Arabia. ***Ann Saudi Med*** 2016; 36: 313-320.
11. Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. ***Lancet*** 2020; 395: 575-590.
12. Eun TJ, Perkins RB. Screening for cervical cancer. ***Med Clin North Am*** 2020; 104: 1063-1078.
13. Anfinan N, Sait K. Indicators of survival and prognostic factors in women treated for cervical cancer at a tertiary care center in Saudi Arabia. ***Ann Saudi Med*** 2020; 40: 25-35.
14. Sait K, Bentley J, Anfinan N, Power P. Cervical cancer prevention in Saudi Arabia: It is time to call for action. ***The Open Women's Health Journal*** 2012; 6: 1-5.
15. Sankaranarayanan R, Basu P, Wesley RS, Mahe C, Keita N, Mbalawa CCG, et al. Accuracy of visual screening for cervical neoplasia: Results from an IARC multicentre study in India and Africa. ***Int J Cancer*** 2004; 110: 907-913.
16. Hirth J. Disparities in HPV vaccination rates and HPV prevalence in the United States: a review of the literature. ***Hum Vaccin Immunother*** 2019; 15: 146-155.

17. Itarat Y, Kietpeerakool C, Jampathong N, Chumworathayi B, Kleebkaow P, Aue-Aungkul A, et al. Sexual behavior and infection with cervical human papillomavirus types 16 and 18. ***Int J Womens Health*** 2019; 11: 489-494.
18. Pimple S, Mishra G. Cancer cervix: Epidemiology and disease burden. ***Cytojournal*** 2022; 19: 21.
19. Huber J, Mueller A, Sailer M, Regidor PA. Human papillomavirus persistence or clearance after infection in reproductive age. What is the status? Review of the literature and new data of a vaginal gel containing silicate dioxide, citric acid, and selenite. ***Womens Health (Lond)*** 2021; 17: 17455065211020702.
20. Krings A, Boateng G, Dunyo P, Amuah J, Adams R, Adunyame L, et al. Dynamics of genotype-specific HPV clearance and reinfection in rural Ghana may compromise HPV screening approaches. ***Papillomavirus Res*** 2019: 7: 45-51.
21. Tekalegn Y, Sahiledengle B, Woldeyohannes D, Atlaw D, Degno S, Desta F et al. High parity is associated with increased risk of cervical cancer: Systematic review and meta-analysis of case-control studies. ***Womens Health (Lond)*** 2022; 18: 17455065221075904.
22. Anastasiou E, McCarthy KJ, Gollub EL, Ralph L, van de Wijgert JHHM, Jones HE. The relationship between hormonal contraception and cervical dysplasia/cancer controlling for human papillomavirus infection: A systematic review. ***Contraception*** 2022; 107: 1-9.
23. Duong LM, Pham LV, Pham TT, Tran DN, Bui NQ, Tran H Do, et al. DNA-HPV transition rate and related factors in HPV-infected women in Can Tho city, Vietnam. ***Trop Med Int Health*** 2019; 24: 1330-1334.
24. Obaid ZM, Amer AW, Zaky MS, Elhenawy RM, Megahed AEM, Hanafy NS, et al. Prevalence of female sexual dysfunction among diabetic females: a cross- sectional case controlled study. ***Postgrad Med*** 2022; 134: 680-685.
25. Gul R, Gul S, Khan MA, Satti RRUH. Sexual dysfunction: Prevalence and relationship with depression and other socio-demographic factors among the type 2 diabetic women of Pakistan. ***J Pak Med Assoc*** 2021; 71: 2515-2518.
26. Santana LM, Perin L, Lunelli R, Inácio JFS, Rodrigues CG, Eibel B, et al. Sexual dysfunction in women with hypertension: a systematic review and meta-analysis. ***Curr Hypertens Rep*** 2019; 21: 25.
27. Murfin J, Irvine F, Meechan-Rogers R, Swift A. Education, income and occupation and their influence on the uptake of cervical cancer prevention strategies: A systematic review. ***J Clin Nurs*** 2020; 29: 393-415.
28. Pauli S, Kops NL, Bessel M, Lina Villa L, Moreno Alves Souza F, Mendes Pereira GF, et al. Sexual practices and HPV infection in unvaccinated young adults. ***Sci Rep*** 2022; 12: 12385.
29. Nielsen NM, Davidsen RB, Hviid A, Wohlfahrt J. Divorce and risk of hospital-diagnosed infectious diseases. ***Scand J Public Health*** 2014; 42: 705–711.