CLINICAL ARTICLE

Risk factors for human papillomavirus infection among women in Portugal: The CLEOPATRE Portugal Study

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ABSTRACT

Objective: To investigate demographic, socioeconomic, lifestyle, and medical factors that might predispose women to cervical human papillomavirus (HPV) infection. Method: A cross-sectional population-based study was performed. Women aged 18–64 years who attended selected obstetrics and gynecology or sexually transmitted disease (STD) clinics in mainland Portugal between February 2008 and March 2009 were recruited, according to an age-stratified sampling strategy. Liquid-based cytology samples were analyzed centrally for HPV genotype and for cytologic features. Univariate and multivariate logistic regression analyses identified risk factors for HPV infection. Results: Among the 2326 women evaluated, the crude prevalence of HPV infection was 19.4%. Lifetime number of sexual partners was a strong predictor of HPV infection (odds ratio 5.44 for 5–10 partners versus 1 partner; $P<0.001$). Other risk factors were young age (particularly among women aged 20–24 years; $P<0.001$); country of birth other than mainland Portugal ($P=0.002$); education up to secondary school level ($P=0.010$); smoking history (≤ 10 years; $P=0.004$); and any STD in the past 12 months ($P=0.052$). Conclusion: Data from the present study may aid identification of women at increased risk of HPV infection and target prevention strategies.

Trial registration: National Commission of Data Protection (CNPD) registration number 5346/2007; Sanofi Pasteur MSD study number HPV-E05.

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1. Introduction

Infection with human papillomavirus (HPV) is an obligatory event for the development of cervical cancer [1]. Specific HPV genotypes (HPV 6, 11, 16, and 18) are responsible for the majority of anogenital diseases caused by this virus among women [2,3].

Infection with high-risk HPV genotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) in the presence of risk factors that promote the persistence of infection precedes the development of precancerous lesions of the cervix. These risk factors are either biological, such as co-infections with other sexually transmitted diseases (STDs), or behavioral, such as sexual habits. A consistent association has been demonstrated between an increased lifetime number of sexual partners and HPV infection among women [4–6]. However, a number of other factors, such as young age at first sexual intercourse, use of oral contraceptives, and smoking have shown inconsistent associations with HPV infection [6–9].

The CLEOPATRE (Cervical LEsions Observed by PApillomavirus Types – a Research in Europe) studies aim to provide a better understanding of the epidemiology of HPV infection across Europe. Based on data for a sample of women attending gynecology/obstetrics or

STD clinics, the CLEOPATRE Portugal study has estimated the overall, age-stratified and type-specific prevalence of cervical HPV infection in women aged 18–64 years living in mainland Portugal [10]. The objective of the present analysis was to assess demographic, socioeconomic, lifestyle, and medical factors that may predispose women enrolled in the CLEOPATRE Portugal study to cervical HPV infection.

2. Materials and methods

The CLEOPATRE Portugal study was a population-based, observational, cross-sectional study conducted between February 1, 2008, and March 31, 2009, across the 5 Regional Health Administrations of mainland Portugal. The study methods have been described in detail previously [10]. Briefly, women aged 18–64 years attending selected obstetrics and gynecology or STD clinics and who had not been vaccinated against HPV were invited to participate in the study. Pregnant women for whom a Papanicolaou test was not contraindicated were eligible to participate. Virgins and women with a history of abnormal cytology in the 12 months before the enrolment visit, who had undergone a hysterectomy and or who had undergone a cone excision or loop electrosurgical excision procedure in the 24 months before the enrolment visit, were excluded from participation. The protocol was approved by the National Institute of Health (INSA), which was the public entity responsible for the present epidemiologic study. Study procedures were approved by the Ethics Committee of each collaborating Center. All participants were informed about the procedures and data handling, and a signed consent form was obtained prior to any study procedure.

After enrollment, demographic, socioeconomic, lifestyle, and medical details were collected and recorded in a case report form. Liquid-based cytology samples were collected during a gynecologic examination and sent to a centralized laboratory for HPV genotyping and cytologic evaluation. Genotyping was performed using the CLART HPV 2 assay (GENOMICA, Madrid, Spain). This methodology uses biotinylated primers that amplify a fragment of 450 bp within the HPV L1 ORF region. Co-amplification of an 892-bp region of the *CFTR* gene and a 1202-bp fragment of a transformed plasmid provides a control to ensure DNA adequacy and PCR efficiency. Amplicons are detected by hybridization in a low-density microarray containing triplicate DNA probes specific to 35 genotypes (HPV 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 68, 70, 71, 72, 73, 81, 82, 83, 84, 85 and 89). Semi-quantitative results can be obtained in an automatic reader. DNA was isolated from 1 mL of cellular suspension using the NucliSENS easyMAG (BioMerieux, Boxtel, The Netherlands) system, as specified in the manufacturer's instructions. Cytologic evaluation was performed on the liquid-based samples using the ThinPrep method (Cytyc, Boxborough, MA, USA), and cytology slides were classified according to the Bethesda System.

Statistical analyses were undertaken at the Department of Epidemiology of INSA using Basic and Complex Samples from SPSS version 17.0 (IBM, Armonk, NY, USA), as described previously [10]. Univariate logistic regression analysis was conducted to evaluate the association between HPV infection (dependent variable) and potential risk factors (explanatory variables). The potential risk factors evaluated were age; country of birth; level of education; smoking habits; age at first sexual intercourse; contraceptive use; lifetime number of sexual partners; any circumcised sexual partner; history of cervical intraepithelial neoplasia; any STD in the past 12 months; and current status of the immune system. The relative risk estimation (odds ratio [OR] with 95% confidence interval [CI]) is presented for each explanatory variable.

The multivariate logistic regression model (Pearson χ^2 test) between HPV infection and the explanatory variables was adjusted for the variables used in the study design (age group and Regional Health Administration) and for the variables identified as statistically

significant ($P<0.05$) in the univariate analysis. Using a "forward conditional" method [11], explanatory variables demonstrating statistical significance in the univariate analyses were entered in sequence into the multivariate regression equation. A P value of less than 0.05 was considered statistically significant.

3. Results

A total of 2372 women were invited to participate in the study and provided informed consent. One woman was withdrawn by one of the study investigators, and 45 women were excluded on the basis of the defined exclusion criteria. In all, 2326 women were included in the analysis; the mean age of the study group was 32.6 ± 14.1 years, while the median age was 27 years. The majority of women were born in Portugal (n = 2210; 95.0%); 800 (34.4%) had a university or college education; and 518 (22.3%) were smokers. Over half of the study population had children (n = 1277; 54.9%) and 2072 (89.1%) reported using contraception. Most women reported a single lifetime sexual partner (n = 1333; 57.3%); 2246 (96.6%) reported the absence of any STD in the past 12 months; 2234 (96.0%) had no history of cervical intraepithelial neoplasia; and 2277 (97.9%) were not currently immunocompromised.

The overall prevalence of HPV in the study sample was previously reported as 19.4% (n = 451; 95% CI 17.8–21.0) [10]. Prevalence by age group ranged from 28.8% (199/691) among women aged 20–24 years to 5.6% (11/196) among those aged 60–64 years. High-risk HPV genotypes were identified in 76.5% (345/451) of the HPV-positive women, with the highest prevalence among the younger age groups (18–29 years) [10]. Infection with multiple HPV genotypes was observed in 7.1% (165/2326) of the study population and 36.6% (165/451) of the HPV-positive women [10].

The results of the univariate logistic regression analysis of HPV infection status versus demographic, socioeconomic, lifestyle, and medical variables is shown in Table 1. Young age increased the risk of HPV infection, with the highest risk occurring in the 20–24 years age group. Compared with the 60–64 years age group, the OR was 6.80 (95% CI, 0.87–3.90). Women born outside mainland Portugal also had an increased risk of HPV infection, as did women educated up to secondary school level.

Smoking was associated with an increased risk of HPV infection, with an OR of 2.18 (95% CI, 1.73–2.75), while ex-smokers had a marginally increased risk (OR 1.13; 95% CI, 0.80–1.59), although this finding was not statistically significant. Among current smokers, the risk of HPV infection increased with the number of cigarettes smoked. However, compared with women who had smoked for up to 10 years, women who had smoked for longer (11–20 years and ≥21 years) had a lower risk of HPV infection. Young age at first sexual intercourse and a high lifetime number of sexual partners were both strongly associated with the prevalence of HPV infection. Use of contraception increased the risk of HPV infection (OR 2.12; 95% CI, 1.40–3.20) as did having a circumcised sexual partner (OR 1.72, 95% CI 1.27–2.34). Women without STDs in the past 12 months had a lower risk of HPV infection; the OR was 0.31 (95% CI, 0.18–0.53).

The association between age and HPV infection remained statistically significant in the multivariate logistic regression analysis (Table 2). The highest risk of HPV infection was observed among women aged 20–24 years, whose risk of infection was 3-fold higher than that of women aged 60–64 years. The OR for this association was 3.02 (95% CI, 1.52–6.00; $P=0.002$). Women born outside mainland Portugal showed a 2-fold higher risk of infection, with an OR of 2.00 (95% CI, 1.30–3.06; $P=0.002$). Women educated up to basic or secondary school level continued to show an increased risk of HPV infection compared with women with a college or university education. The OR in the 12th year was 1.47 (95% CI, 1.11–1.95; $P=0.007$), while the OR in the 9th year was 1.57 (95% CI, 1.16–2.13, $P=0.004$). Similarly, women smoking for longer than 10 years continued to show a

Table 1
Univariate logistic regression analysis between HPV infection and the explanatory variables.

Explanatory variable	No. of participants	HPV positive (any genotype) [a]	OR (95% CI) [b]	P value
Age, y	2326			<0.001
60–64	196	11 (5.6)	1.00	
50–59	228	13 (5.7)	1.02 (3.20–12.09)	
40–49	223	22 (9.9)	1.84 (3.62–12.77)	
30–39	256	32 (12.5)	2.40 (2.46–8.98)	
25–29	458	100 (21.8)	4.70 (1.18–4.90)	
20–24	691	199 (28.8)	6.80 (0.87–3.90)	
18–19	274	74 (27.0)	6.22 (0.45–2.32)	
Country of birth	2326			<0.001
Portugal	2210	400 (18.1)	1.00	
Other	116	51 (44.0)	3.55 (2.42–5.20)	
Level of education	2323			<0.001
University/college	800	144 (18.0)	1.00	
Secondary school (10th–12th year)	587	155 (26.4)	1.64 (1.26–2.11)	
Basic school (5th–9th year)	500	119 (23.8)	1.42 (1.08–1.87)	
Primary school (1st–4th year)	351	30 (8.5)	0.43 (0.28–0.65)	
No formal education or incomplete (4th year)	85	3 (3.5)	0.17 (0.05–0.54)	
Smoking status	2311			<0.001
Never smoked	1524	246 (16.1)	1.00	
Current smoker	518	153 (29.5)	2.18 (1.73–2.75)	
Ex-smoker	269	48 (17.8)	1.13 (0.80–1.59)	
Current smokers: length of smoking history, y	512			<0.001
1–10	385	137 (35.6)	1.00	
11–20	79	11 (13.9)	0.29 (0.15–0.57)	
≥21	48	5 (10.4)	0.21 (0.08–0.54)	
Current smokers: no. of cigarettes smoked	518			0.380
<7 weekly	91	21 (23.1)	1.00	
1–9 daily	231	68 (29.4)	1.39 (0.79–2.44)	
10–20 daily	178	57 (32.0)	1.57 (0.90–2.81)	
>20 daily	18	7 (38.9)	2.12 (0.73–6.16)	
Age at first sexual intercourse, y	948			<0.001
≥25	30	4 (13.3)	1.00	
21–24	113	15 (13.3)	1.00 (0.30–3.25)	
19–20	162	39 (24.1)	2.06 (0.68–6.27)	
17–18	351	89 (25.4)	2.21 (0.75–6.50)	
15–16	230	64 (27.8)	2.51 (0.84–7.46)	
≤14	62	25 (40.3)	4.39 (1.37–14.13)	
Prior pregnancies	2326			<0.001
Yes	1277	194 (15.2)	1.00	
No	1049	257 (24.5)	1.81 (1.47–2.23)	
Contraceptive use	2322			0.001
No	250	27 (10.8)	1.00	
Yes	2072	423 (20.4)	2.12 (1.40–3.20)	
Type of contraceptive				
Oral contraceptive	1778	377 (21.2)	1.45 (1.04–2.03)	
Intrauterine device	203	23 (11.3)	0.47 (0.30–0.73)	
Condom	618	133 (21.5)	1.10 (0.87–1.39)	
Tubal ligation	102	6 (5.9)	0.23 (0.10–0.54)	
Other method	63	3 (4.8)	0.19 (0.06–0.61)	
Lifetime number of sexual partners	2287			<0.001
1	1333	131 (9.8)	1.00	
2–4	834	257 (30.8)	4.09 (3.24–5.16)	
5–10	120	58 (48.3)	8.58 (5.75–12.82)	
Any circumcised sexual partner	2166			0.001
No	1928	351 (18.2)	1.00	
Yes	238	66 (27.7)	1.72 (1.27–2.34)	
Any sexually transmitted disease in the past 12 mo	2304			<0.001
Yes	58	25 (43.1)	1.00	
No	2246	426 (19.0)	0.31 (0.18–0.53)	
Retroviral disease	58			<0.001
Yes	7	1 (14.3)	1.00	
No	51	24 (47.1)	5.33 (0.60–47.52)	
Herpes	58			<0.001
Yes	7	3 (42.9)	1.00	
No	51	22 (43.1)	1.01 (0.21–4.99)	
Genital warts	58			<0.001
Yes	20	10 (50.0)	1.00	
No	38	15 (39.5)	0.65 (0.22–1.94)	
Hepatitis	58			<0.001
Yes	4	3 (75.0)	1.00	
No	54	22 (40.7)	0.23 (0.02–2.35)	
Other sexually transmitted disease	58			<0.001
Yes	23	11 (47.8)	1.00	
No	35	14 (40.0)	0.73 (0.25–2.10)	

Table 1 (*continued*)

Explanatory variable	No. of participants	HPV positive (any genotype) [a]	OR (95% CI) [b]	P value
History of cervical intraepithelial neoplasia	2298			0.878
No	2234	436 (19.5)	1.00	
Yes	64	12 (18.8)	0.95 (0.50–1.80)	
Currently immunocompromised	2305			0.849
Yes	28	5 (17.9)	1.00	
No	2277	441 (19.4)	1.11 (0.42–2.92)	

Abbreviations: CI, confidence interval; HPV, human papillomavirus; OR, odds ratio.
[a] Values are given as number (percentage).
[b] An OR of 1.00 represents the null hypothesis of no association.

lower risk of HPV infection than women who had smoked for up to 10 years. Among women who had smoked for 11–20 years, the OR was 0.42 (95% CI, 0.20–0.87; $P = 0.019$), whereas the OR for women who had smoked for 21 years or more was 0.50 (95% CI, 0.18–1.41; not significant). A high lifetime number of sexual partners remained a significant predictor of HPV infection, with more than a 5-fold increased risk in women with 5–10 sexual partners compared with women reporting 1 lifetime sexual partner. The OR for this association was 5.44 (95% CI, 3.51–8.43; $P < 0.001$). Women reporting any STD in the past 12 months showed an increased risk of HPV infection

Table 2
Multivariate logistic regression analysis between HPV infection (any genotype) and the explanatory variables.[a]

Explanatory variable	No. of participants	OR (95% CI) [b]	P value
Age, y	2295		<0.001
60–64	192	1.00	
50–59	221	0.96 (0.42–2.23)	
40–49	215	1.36 (0.62–2.97)	
30–39	252	1.46 (0.69–3.10)	
25–29	456	2.32 (1.15–4.67)	
20–24	686	3.02 (1.52–6.00)	
18–19	273	2.50 (1.22–5.13)	
Country of birth	2295		0.002
Portugal	2179	1.00	
Other	116	2.00 (1.30–3.06)	
Level of education	2295		0.010
University/college	791	1.00	
Secondary school (10th–12th year)	583	1.47 (1.11–1.95)	
Basic school (5th–9th year)	493	1.57 (1.16–2.13)	
Primary school (1st–4th year)	344	1.10 (0.68–1.77)	
No formal education or incomplete (4th year)	84	0.53 (0.16–1.82)	
Current smokers: length of smoking history, y	510		0.004
1–10	384	1.00	
11–20	78	0.42 (0.20–0.87)	
≥21	48	0.50 (0.18–1.41)	
Lifetime number of sexual partners	2260		<0.001
1	1312	1.00	
2–4	828	3.10 (2.42–3.97)	
5–10	120	5.44 (3.51–8.43)	
Any sexually transmitted disease in the past 12 mo	2295		0.052
No	2237	1.00	
Yes	58	1.79 (1.00–3.23)	

Abbreviations: CI, confidence interval; HPV, human papillomavirus; OR, odds ratio.
[a] The multivariate logistic regression analysis was adjusted for age group and Regional Health Administration. Explanatory variables were identified as statistically significant ($P < 0.05$) in the univariate analysis.
[b] An OR of 1.00 represents the null hypothesis of no association. Model evaluation: $P = 0.368$ (Hosmer and Lemeshow test); $P < 0.001$ (omnibus test of model coefficients); Nagelkerke $R^2 = 0.205$.

(OR 1.79; 95% CI 1.00–3.23) and this observation bordered on statistical significance ($P = 0.052$).

4. Discussion

A risk factor analysis was carried out as part of the CLEOPATRE Portugal study, a population-based study that aims to evaluate the prevalence of cervical HPV infection among women living in mainland Portugal [10]. The present study evaluated a range of demographic, socioeconomic, lifestyle, and medical variables for their potential to predict the likelihood of HPV infection. The variables identified as risk factors for HPV infection were young age; country of birth other than Portugal; secondary level of education; a smoking history of up to 10 years; a high lifetime number of sexual partners; and any STD in the last 12 months.

The risk of HPV infection was highest among women aged 20–24 years but declined with increasing age. The identification of age as a significant predictor of HPV infection was expected, as it is well recognized that young adults have an increased risk of acquiring HPV, and that HPV prevalence decreases with age [12–14]. In Latin American countries, a second peak of HPV prevalence has been detected among older age groups (≥45 years) [15,16]. In agreement with other European data [12,16], no second prevalence peak was observed in the present study [10].

Lifetime number of sexual partners was identified as a strong determinant of HPV infection in the multivariate analysis. Women reporting 5–10 sexual partners had a 5.44-fold higher risk of infection than women reporting 1 partner. This observation is consistent with the findings of an Italian study conducted in women aged 18–24 years, which showed that women with 5 or more sexual partners in the previous 3 years had a 6.8-fold increased risk of infection compared with women with 1 partner [17].

In terms of smoking habits, there was an apparent protective effect among women who had been smoking for more than 10 years compared with women who had been smoking for a shorter period of time. The number of cigarettes smoked each day or week did not affect the risk of HPV infection in the multivariate analysis. These findings differ from those of other studies that have examined the relationship between smoking and HPV infection. The study in young women in Italy [17] demonstrated a 2-fold higher risk of infection among women smoking more than 10 cigarettes per day compared with non-smokers. Similarly, after adjusting for the lifetime number of sexual partners in a pooled analysis by the International Agency for Research on Cancer (IARC), the risk of HPV infection increased with smoking intensity [9]. The increased prevalence of HPV infection observed in women with a shorter versus a longer smoking history in the present study would suggest that the effects of age may be overriding the effects of smoking.

Compared with women born in mainland Portugal, the risk of HPV infection was doubled among women born elsewhere. The most frequent countries of birth other than Portugal, in descending order, were Portuguese-speaking African countries, Brazil, and eastern European countries. This finding might be related to the fact that the adjusted HPV prevalence is high in these regions [15].

Analysis of the impact of education level on the acquisition of HPV infection revealed that women educated up to secondary school level had the highest risk of infection. In an analysis of data from 2 large multicenter IARC studies, no association between education level and HPV infection emerged [18]. Education level alone is an inadequate measure of socioeconomic status, which is influenced by a combination of other factors. In the IARC analysis [18], an increase in the incidence of cervical cancer among women of low socioeconomic status was attributed largely to age at first sexual intercourse, age at first pregnancy, and parity. The association between secondary level education and HPV infection observed in the present study is probably related to age, with younger women being more likely to report attainment of secondary level education.

As for similar studies, there are some potential limitations and a risk of data bias in the present study, particularly in relation to the explanatory variables "age at first sexual intercourse," "lifetime number of sexual partners," and "any circumcised sexual partner." These variables cover aspects of sexual behavior that women may feel sensitive about, or be uninformed about, and the responses to these questions may not have been answered accurately by some women. Data collection for the variable "age at first sexual intercourse" was introduced after the study had already started, and therefore early study entrants were not questioned on this variable. Although this variable was statistically significant in the univariate model, it was excluded from the multivariate analysis because the number of responses was low. The questions relating to "any circumcised sexual partner" (small number of cases to draw conclusions) and "contraceptive use" were considered to have been formulated inadequately. As a consequence, the risks associated with these variables should be interpreted with caution.

In conclusion, the CLEOPATRE Portugal study has identified a number of demographic, socioeconomic, lifestyle, and medical factors that may help predict cervical HPV infection among women in Portugal. Lifetime number of sexual partners was identified as a major risk factor for HPV infection. Other notable risk factors were birth in countries other than mainland Portugal and a history of any STD in the past 12 months. These data will contribute to a better understanding of the wide spectrum of HPV infection across Europe, and may contribute to the identification of women at increased risk of HPV infection.

Acknowledgments

Conflict of interest

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