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Prevalence of genital HPV infection among women screened for cervical cancer

ABSTRACT

OBJECTIVE: To assess the prevalence of high-risk genital human papillomavirus (HPV) infection by age group and risk factors associated.

METHODS: Cross-sectional study in a sample of 2,300 women (15-65 years old) who self-referred to cervical cancer screening in Sao Paulo and Campinas, Southeastern Brazil, between February 2002 and March 2003. An epidemiological questionnaire was applied and cervical specimens were obtained for cytology and hybrid capture II test (HCII) for HPV detection. Statistical analysis included Pearson Chi-square and unconditional multiple logistic regression model (forward likelihood ratio).

RESULTS: High-risk genital HPV infection prevalence in this sample was 17.8% and age distribution was as follows: 27.1% (<25 years), 21.3% (25-34 years), 12.1% (35-44 years), 12.0% (45-54 years) and 13.9% (55-65 years). Subjects with the highest number of lifetime sexual partners had the highest rates of genital HPV infection. To be living with a partner, aged 35 to 44 years, and former smokers were protective factors. High-risk genital HPV infection was 14.3% in normal cytology, 77.8% in high grade squamous intraepithelial lesions and in the two cases (100%) of cervical cancer.

CONCLUSIONS: High-risk HPV prevalence was high in the sample studied. The highest prevalence of HPV infection was seen in women under 25 years old and then a new increase was seen over the age of 55 and the highest rates were found among those with many sexual partners during their lifetime.

KEY WORDS: Papillomavirus infections, epidemiology. Uterine cervical neoplasms, prevention & control. Risk factors. Cross-sectional studies.

INTRODUCTION

The relationship between cervical cancer and human papillomavirus (HPV) infection has been well established. High-risk HPV DNA is detected in most specimens (92.9% to 99.7%) of invasive cervical cancer.[3,25]

High-risk HPV infection is a requirement, though not exclusive, for the development of cervical cancer. Other factors such as high parity, prolonged oral contraceptive use and smoking[25] can also influence its development. HPV usually infects young people at their early sexual life and it is usually a transient phenomenon in around 80% of cases. However, a small proportion of women will have persistent infection, probably due to inadequate immunological response leading to changes in the cervical epithelium and malignant transformation. Women with persistent infection by different subtypes of high-risk HPV are the actual risk group for the development of cervical cancer.[3]

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There are about 40 different subtypes of HPV infecting the genital tract through sexual exposure. HPV has now become the most common sexually transmitted disease (STD).[24] However, its prevalence varies widely in different populations (ranging from 1.4% to 25.6%) as well as the frequency of occurrence of different virus subtypes.[6]

The number of sexual partners during a lifetime is a major risk factor associated to HPV infection. Other factors include partners' practices and male partner's age compared to women's age with increased risk as partner's age increases.[1]

It is not yet clear how aging affects HPV prevalence in different populations worldwide. Many studies have reported that the highest prevalences occur in women under 25; they then progressively and linearly decline after the age of 25; and remain below 5% after the age of 55.[4,9,10,15,18,20]

Lower prevalences with aging could be explained by changes in sexual practices which would make women less exposed to infection. Yet some studies reported lower prevalence of HPV infection with aging even though in women who show intense, continuous sexual behavior. This suggests that declining prevalences are unrelated to sexual practices and seem to be more related to the development of a type-specific immune response to HPV infection.[4,15]

A second pattern of genital HPV infection prevalence has been described in population-based studies. Prevalence was found to follow a bimodal U-shape curve where higher rates are seen in young people, they then decline in the third decade of like and have a new rise around the age of 55 or more.[12,13,16] The virus subtype involved in the second prevalence rise was different in these studies: low-risk HPV types prevailed in some of them[12,13] while high-risk HPV types were more prevalent in other studies.[11,16]

The reasons for the second rise in prevalence seen in postmenopausal women have not yet been elucidated. It is reasonable to assume that there are several non-excludent mechanisms involved: in a cohort effect, this data could reflect different exposure to HPV over generations;[5,12] or reactivation of latent infection due to progressive type-specific immune response failure; or even a new infection transmitted by either a new sexual partner or the steady one.[24] Age-related hormonal changes should also be considered as they could change women's susceptibility to infection.[16] The transmenopausal and postmenopausal periods are characterized by a progressive significant reduction in ovarian steroidal hormone production which affects the urogenital tract and may predispose to increased risk of infections.[16]

The impact of the second rise in HPV infection on cervical carcinogenesis in women in their fifth decade of life is not yet known.[5] Cervical cancer has been associated to persistent high-risk HPV infection acquired by women during their childbearing years. However, understanding the natural history of HPV infection at different stages of female life is crucial for the development of effective strategies for cervical cancer prevention suitable for all age groups.[13]

The objective of the present study was to assess the prevalence of high-risk genital HPV infection by age groups and its risk factors associated in women screened for cervical cancer.

METHODS

The present analysis is part of a longitudinal study Latin America Screening Study (LAMS).[a] The LAMS was a multi-centre screening trial with three centers in Brazil (São Paulo, Campinas and Porto Alegre) and one center in Argentina. LAMS aimed to compare different screening tools (cervical cytology as conventional PAP and Liquid Based Cytology, Hybrid Capture II, visual inspection with acetic acid) in screening of precursors cervical cancer lesions and in cervical cancer in these two countries.

This is a cross sectional study with preliminary results from two cities, São Paulo and Campinas, Southeastern Brazil. A sample of 2,300 women was selected from 5,634 subjects to perform high-risk HPV types detection by Hybrid Capture II (HCII), between February 2002 and March 2003.

The study included women between 15 to 65 years old, with intact uterus (i. e. no previous surgical procedure of the cervix) and who had sought cervical cancer prevention services. The exclusion criteria were: any confirmed or clinically suspected immunosuppression, women under treatment for genital condyloma, women with diagnosis or under treatment for cervical intra epithelial neoplasia or any gynaecological cancer, mental deficiency and pregnant women.

An epidemiological structured questionnaire was applied to obtain sociodemographic, behavior and reproductive information. A pelvic examination was performed to obtain cervical specimen for conventional Pap or liquid based cytology and HCII test for HPV detection.

Cervical cytology was tested in two modes: conventional and liquid based cytology techniques. Liquid based cytology was tested in cervical samples only in São Paulo centre (1,628 women). Conventional cytological smears were obtained from ectocervix

[a] Unpublished data.

and endocervix, collected with Ayre spatula and endocervical brush. The slides were immediately fixed in polietilenoglicol and stained with conventional Papanicolaou method.

Liquid based cytology were collected using the brush of the DNA-Citoliq System (Digene do Brasil), and immersed in the UCM (Universal Collecting Medium, Digene do Brasil) vials. The sample processing followed the manufacturer's instructions as described in previous studies.[22]The slides were stained with conventional Papanicolaou method. Cytological results were reported according to the Bethesda System Terminology 2001.[21]

Cytological slides were read at the Pathology Division, Instituto Adolfo Lutz, São Paulo and Department of Pathology of Hospital da Faculdade de Ciências Médicas da Universidade Estadual de Campinas. Cytological samples were periodically subjected to external quality control, in two laboratories in Italy and Slovenia.

HPV DNA detection was made by Hybrid Capture 2 (HCII) assay, using cervical swabs. The samples were analysed only for the presence of high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. The usual limit of 1 pg/ml of HPV16 DNA was used as the positive control (CO). Samples were classified as high-risk HPV positive, if the relative light unit (RLU) reading of the luminometer was equal to or greater than the mean of CO values, i.e., RLU/CO $\geq$1.0 pg/ml being the cut-off for test positivity.[17]

Detection rates of HPV DNA using CHII and prevalences of cytological abnormalities were described as percentages. To explore factors associated to HPV infection univariate analysis and Pearson's chi-square test at a 5% significance level were conducted.

The multivariate analysis included a logistic regression model where the variable was response to HPV infection and explanatory variables were those statistically significant in the chi-square test. A forward likelihood ratio approach was applied for variable selection.[14] Odds ratios (OR) and their related 95% confidence intervals were estimated.

The study protocol was approved by the research ethics committees of the Hospital Maternidade Leonor Mendes de Barros, Faculdade de Ciências Médicas da Universidade Estadual Campinas and the Comissão Nacional de Ética. The protocol was submitted and approved by the Comitê de Ética em Pesquisa, Universidade de São Paulo.

The participants signed informed consent form. Women with abnormal cytological results were followed and treated if necessary.

RESULTS

Subjects' mean age was 35.7 (SD ±10.6) years with the following age distribution: 19.8% (457) were under 25 years; 28.1% (647) 25–34 years; 29.6% (683) 35–44 years; 19.1% (441) 45–54 years; and 3.1% (72) 55–65 years. The study sample description by sociodemographic, sexual and reproductive characteristics are shown in Table 1. This table also shows the variables significantly associated to HPV infection in the univariate analysis.

The prevalence of high-risk genital HPV infection in the whole sample was 17.8%. The prevalence by age groups was as follows: 27.1% (under 25 years); 21.3% (25–34 years); 12.1% (35–44 years); 12.0% (45–54 years); and 13.9% (55–65 years). This prevalence was 14.3% in women with normal cytology. The Figure illustrates the distribution of high-risk genital HPV infection prevalences by age group in all subjects and the prevalences in women with normal cytology (N=2,080).

Of all cytology samples collected, 3 (0.1%) were excluded due to technical problems. Of 2,297 studied, 13 (0.5%) were deemed inadequate. Normal cytology results were found in 90.5%. Cytological abnormalities were detected in 204 (8.8%) of the samples studied: 5.31% of ASCUS (atypical squamous cells of undetermined significance including potentially non-neoplasic lesions and those where high-grade squamous intraepithelial lesion cannot be excluded), followed by 2.0% of LSIL (low-grade squamous intra-epithelial lesion), 1.17% of HSIL (high-grade squamous intra-epithelial lesion), and two carcinomas (0.08%). CHII test was positive in 14.3% of all cytology samples and 52.4% of 204 smears with any cytology abnormality (Table 2).

Women under 35 years old had the highest rates of all cytology abnormalities including: LSIL (71.7%), and ASCUS (57.3%) as well as HSIL (70.3%) (Table 2).

The multivariate analysis revealed the following independent variables: in the age groups 25–34 years, 35–44, 45–54, and 55 years or more there was a negative association with infection when compared to young women under 25. However, this association was statistically significant only in those aged 35–44 years. Living with a single partner was associated to infection protection. The number of partners (2 to 3, and 4 or more) during a lifetime remained a major risk factor with OR=1.9428 (95% CI: 1.48; 2.55) and OR=2.3918 (95% CI:1.75; 3.28) respectively compared to monogamous subjects. Being a former smoker had a negative association with HPV infection (Table 3). There was no association between high-risk HPV infection and the following variables: race, schooling, age at sexual initiation, number of sexual partners in the previous year, use of hormonal contraception, length of hormonal contraception use, prior Papanicolaou smears, and past history of partner's STD.

Table 1. Demographic, behavioral and reproductive variables and high-risk genital HPV infection. São Paulo and Campinas, Southeastern Brazil, 2002–2003.

Variable	Category	% HPV+	HPV+/ Total	p-value**
Age (years)	≤ 25	27.1	124/457	<0.001
	25–34	21.3	138/647	
	35–44	12.1	83/683	
	45–54	12.0	53/441	
	55–65	13.9	10/72	
Race	White	16.5	252/1,527	0.05
	Black	23.1	48/207	
	Mulatto	19.3	101/522	
	Other	11.8	4/34	
Schooling (years)	≤ 4	13.4	77/ 573	0.005
	5–8	17.7	132/749	
	9–11	19.6	119/607	
	≥ 12	21.8	80/367	
Living with a partner	No	26.2	187/713	<0.001
	Yes	14.0	221/1,584	
Sexual initiation (years)	15	22.7	115/ 508	<0.001
	16–17	21.5	124/577	
	18–19	15.8	84/ 533	
	20	12.5	85/ 678	
Number of sexual partners	1	10.6	110 /1,034	<0.001
	2–3	22.0	179/813	
	≥ 4	26.3	119/452	
Number of sexual partners in the past year	Zero	15.6	29/186	<0.001
	1	16.8	336/2,005	
	2–3	38.1	37/97	
	≥ 4	50.0	6/12	
Hormonal contraception	No	15.2	65/427	<0.001
	Yes	22.8	146/640	
	Other	15.9	196/1,229	
Hormonal contraception (years)	< 5	23.7	93/393	<0.001
	5–9	25.9	36/139	
	10	14.1	15/106	
Previous Papanicolaou	Yes	17.0	362/2,121	0.006
	No	25.3	45/178	
Smoking	Never	18.2	266/1,464	<0.001
	Current	21.8	104/478	
	Past	10.8	38/352	
Sexual partner with STD	No	16.9	336/1,989	0.025
	Yes	22.6	47/208	
	Unknown	24.3	25/103	

* N was different for each variable (varying according to data availability)
** Pearson's chi-square test

Table 2. Odds ratios of independent factors associated to high-risk HPV infection based on the final results of the multivariate logistic regression model. São Paulo and Campinas, Southeastern Brazil, 2002–2003.

Variable	Category	OR	95% CI
Age (years)	< 25	REF	
	25-34	0.7971	0.5934;1.0706
	35-44	0.4346	0.3142;0.6012
	45-54	0.4653	0.3226;1.0000
	55-65	0.5581	0.2724;1.1436
Living with a partner	No	REF	
	Yes	0.6055	0.4767;0.7690
Number of partners	1	REF	
	2 or 3	1.9428	1.4800;2.5502
	4 or more	2.3918	1.7464;3.2756
Smoking	Never smoked	REF	
	Current smoking	1.1246	0.8566;1.4765
	Yes, former smoker	0.5766	0.3959;0.8399

OR of the prevalence adjusted for statistically significant variables in the univariate analysis.

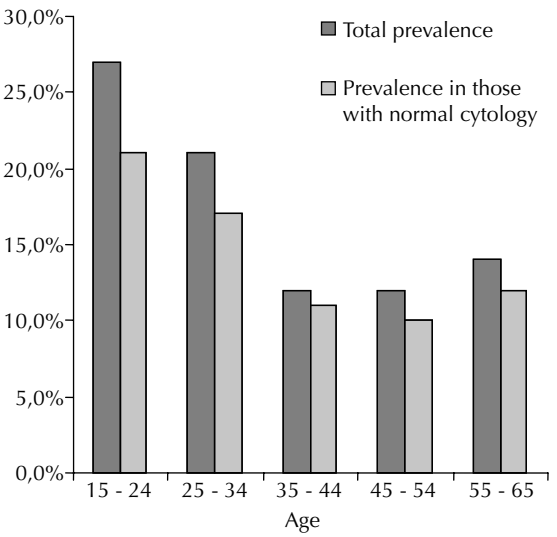

Figure. Prevalence of high-risk HPV genital infection (%), by age group, in all subjects and in those subjects with normal cytology results only. São Paulo and Campinas, Southeastern Brazil, 2002–2003.

DISCUSSION

The present study found a 17.8% prevalence of high-risk genital HPV infection, which is higher than 13.8% for both virus subtypes previously reported in the city of São Paulo[9] and 15.4% found in southern Brazil[22] for high-risk virus subtypes only using also CHII test for HPV detection. The prevalence found was also much higher than that found in studies in Spain (3%) for both

Table 3. Results of cervical cytology compared to hybrid capture II test (HCII) by age groups. São Paulo and Campinas, Southeastern Brazil, 2002–2003.

Cytology result	<35 years	35–54 years	55–65 years	Total HPV+		Total cytology tests
	HPV+/total	HPV+/total	HPV+/total	N	%	
Inflammatory	179/970	111/1,043	8/67	298	14.3	2,080
LSIL	24/33	5/13	0	29	63.0	46
ASCUS	41/70	11/49	0/3	52	43.0	122
AGUS	2/2	1/5	0	3	43.0	7
HSIL	15/19	6/8	0	21	78.0	27
Carcinoma	0	0	2/2	2	100.0	02
Inadequate	0/8	2/5	0	2	15.3	13
Total cytology tests/ age	261/1,102	136/1,123	10/72	407*	100	2,297

LSIL = low-grade squamous intra-epithelial lesion; HSIL = high-grade squamous intra-epithelial lesion; ASCUS = atypical squamous cells of undetermined significance including potentially non-neoplasic lesions and those where high-grade squamous intra-epithelial lesion cannot be excluded; AGUS = atypical glandular cells of undetermined significance.
*Loss of cytology results in subjects with CHII positive.

virus subtypes,[20] Chile (9.1%)[8] and Argentina (12.1%)[18] for high-risk virus subtypes, and slightly lower than that reported in Nigeria (19.7%)[23] for high-risk HPV.

The assessment of high-risk genital HPV infection prevalence by age group showed that women under 25 had the highest prevalence (27.1%), which is consistent with other authors' findings.[10,12,19] This finding confirms what is already known on the natural history of this condition which is characterized by higher infection rates after sexual initiation.

The study results revealed declining rates of high-risk HPV infection after the age of 25. The lowest infection rates were seen in about 12.0% in women aged 35–54 but a new prevalence rise (13.8%) was found in those aged 55–65 years. However, other studies reported after the age of 55 a linear decline in HPV prevalence with age below about 5% for both virus subtypes.[4,10,18] Yet the proportion of women older than 55 was significantly lower compared to the other age groups.

The prevalence distribution was very similar in all age groups studied but with higher rates than those reported in a recent study. There were found higher prevalences in young women for high-risk viruses, i.e., 9.7% and 10.8% in those aged 35–54 and 55–64, respectively.[13]

Studies are still inconsistent on the age at which the second infection rise occurs. The present study detected a rise in the 55–65 age group, which is consistent with the findings of a Costa Rica study[12] but inconsistent with that reported in Mexico where a second rise was seen around the age of 45.[16]

HPV infection is known to be commonly associated to abnormal cytology.[3,11] Thus, high-risk HPV prevalence distribution by age was analyzed in the whole sample and in those women with normal cytology only. After excluding abnormal cytology results, high-risk HPV prevalence remained high in the whole sample (14.3%) compared to 9.9% recently reported by Herrero et al[13] in normal cytology tests as well. In those with normal cytology, after stratifying HPV prevalence by age group, the distribution curve was very similar to that found for the whole sample in the different age groups (Figure).

In Africa, high prevalence of genital HPV infection is seen in all age groups, which could indicate that these populations would have high rates of cervical cancer.[23] Prevalence rise after the age of 55 found in the present study is consistent with the prevalence distribution seen in areas of high rates of cervical cancer.[23] To corroborate this premise, countries with low cervical cancer rates typically have a linear decline of HPV prevalence with age.[20]

The prevalence of genital HPV infection is highly variable in different geographical areas. This could be due to several factors such as study design, sensitivity of virus detection test, virus subtypes studied and socially accepted sexual behaviors. Besides, it should be taken into consideration the effectiveness of cervical cancer screening programs for the diagnosis and treatment of women with HPV-induced lesions.[5]

Since the present study had a cross-sectional design, it did not allow for the differentiation between incident and persistent HPV infection. Of those subjects older than 55, 64% reported having a single sexual partner during the previous year and the remaining reported not having any sexual partner in the previous year, which is suggestive of persistent infection. It is likely that changes in sexual behavior in the last decades have led to different exposures to HPV. This could explain the different prevalences found by age groups and would reflect a specific exposure to HPV in successive birth

cohorts. However, this hypothesis still cannot be either refuted or confirmed due to the lack of historical data on HPV prevalence as well as cohort studies long enough to allow such conclusion.[5,24]

A plausible hypothesis to the high prevalence of HPV infection would be the sexual behavior of male partners. Studies in Latin America showed an association between cervical cancer risk and male partner's sexual practices such as sexual exposure to many female partners, extramarital sex and sex with sex workers.[7] In the present study, partner's STI was reported by 9% of all subjects; however, this variable did not show a statistical significant association with HPV infection.

It is possible that an even higher prevalence of HPV infection would have been found in this study sample if low-risk viruses were also included. Yet the high prevalence of high-risk HPV infection indicates a pressing need for education actions focusing on sexual risk behavior changes to reduce STIs including HPV infection. In addition, there is a need in Brazil to develop effective actions for the detection and follow-up of cervical HPV lesions given their close relationship with cervical cancer.

In regard to factors associated to high-risk genital HPV infection (positive CHII test), in the multivariate analysis, only greater number of sexual partners during a lifetime remained a risk factor. Women reporting two or more partners were more likely to be infected than monogamous subjects, a finding that is corroborated in the literature and consistent with sexual transmission of this infection.[10,13,16,18, 20]

On the other hand, living with a steady single partner and former smokers were variables associated with high risk HPV infection protection. Protection was also seen in women aged 25 or older compared to those under 25. However, this association was statistically significant only in the 35–44 age group. In contrast to these results, for high-risk HPV, there have been reported a linear decline of infection risk with age[18] as well as a marked risk reduction after the age of 30.[10,18,24]

Monogamous women were more protected against infection compared to non-monogamous women as found in previous studies.[4,10,13,20] Possibly women in steady relationships are likely to have stable sexual life and lower exposure to different sexual partners.

Consistent with Bauer et al's findings,[2] compared to smokers, formers smokers had a negative association with HPV infection. Yet Ferreccio et al[8] reported a similar HPV infection risk in both smokers and former smokers. The association between genital HPV infection and smoking, reported in some studies[8] but not corroborated by other studies,[4,10] has yet to be clarified.

Cytology abnormalities detected in 8.8% of cervical smears was similar to that found in a study carried out in a border area between Mexico and the US (9.3%)[10] although higher than 3.6% and 5.7% found in Chile and Spain, respectively, in population-based studies.[8,20]

The most common cytological abnormalities were ASCUS and LSIL. The literature shows these abnormalities are often found in up to 10% of test results provided by cytology laboratories.[24] Adequate diagnosis, management and follow-up of HPV-induced cytological abnormalities are challenging and are a burden to health systems. Previous studies found an association between cytological abnormalities and HPV detection, and while about 11% of women with normal cytology have detectable HPV this proportion can reach as much as 70% of all women with abnormal tests.[12,13]

High HPV prevalence among younger women can reflect transient infection. However, in women aged 30 or more, positive testing can indicate persistent infection and require more careful and frequent follow-up.

The so far accepted pattern of HPV prevalence decline with increasing age indicates that cervical cancer screenings for women after the age of 50 can be performed less frequently but still be accurate and cost-effective.[5] However, this remains a controversial issue as the age to safely discontinue screening for cervical cancer needs to be carefully determined in the light of the second rise in HPV infection in some populations and its potential role in cervical carcinogenesis.

The understanding of the epidemiology of genital HPV infection is crucial for the development of prevention actions against this infection and thus reduction of cervical cancer.[9]

Prospective studies can help establish determinants of infection, infection dynamics and persistence of HPV in different age groups in order to implement prevention actions suitable for all stages of women's life.

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