Brazilian Journal of Microbiology (2022) 53:1979–1986
https://doi.org/10.1007/s42770-022-00849-4

CLINICAL MICROBIOLOGY - RESEARCH PAPER

Prevalence of HPV and associated factors in a population of women living in southern Brazil

Ana Paula Reolon Bortolli[1] · Indianara Carlotto Treco[1] · Valquíria Kulig Vieira[1] · Claudicéia Risso Pascotto[1] · Lirane Elize Defante Ferreto[1] · Guilherme Welter Wendt[2] · Léia Carolina Lucio[1]

Received: 10 June 2022 / Accepted: 12 October 2022 / Published online: 20 October 2022

Abstract

Objective To determine the prevalence of HPV and investigate factors associated with the infection in women in the city of Francisco Beltrão, southwest Paraná, attending the public health system.

Methods This cross-sectional study included 324 women, aged between 18 and 65 years, who were attending public health services for routine gynecological consultation. Interviews were conducted to obtain information about socioeconomic, sexual, gynecological, and life habits. After performing the Papanicolaou test, endocervical brush was employed to detect HPV by polymerase chain reaction with the primers MY09-MY11.

Results The prevalence of HPV was 6.8%, out of which 58.3% presented with cytopathologic alterations. And the presence of current cervical alterations can increase the chances of having HPV by almost 33 times (OR_{adj}: 32.688; $p < 0.001$), recent vaginal infection increased the chances of HPV infection by 2.7 times (OR_{adj}: 2.773; $p = 0.04$). The non-white ethnicity increased HPV infection chances threefold (OR_{adj}: 3.058; $p = 0.039$).

Conclusion The main finding was low prevalence of HPV infection. Factors that may be linked to HPV infection were cervical alterations, recent vaginal infection, and women's ethnicity.

Keywords Human papillomavirus · Sexually transmitted infection · Women's health · Papanicolaou test · Ethnicity

Introduction

The human papillomavirus (HPV) causes the most common sexually transmitted infection (STI) in the world and can infect both skin and mucous membranes, comprising about 220 distinct subtypes [1, 2]. Of these, 40 subtypes have the potential to infect the anogenital tract, of which 12 are defined as high risk for the development of cervical cancer (CC), especially subtypes 16 and 18 [3]. However, CC has a good prognosis if diagnosed and treated early [4].

Worldwide, CC is the fourth most frequently diagnosed cancer and the fourth cause of cancer death in women, with an estimated 604,000 new cases and 342,000 deaths worldwide in 2020 [5]. In the state of Paraná, Brazil, the number of women who died due to cervical cancer was 336 in 2019 [6].

HPV infection occurs through skin microlesions or mucous membranes during sexual intercourse, favoring the entry of the virus into the basal layer of the epithelium cells [7]. Most infections are eliminated or suppressed by immune system-mediated cells between 1 and 2 years; however, persistent infections are strongly linked to the development of precancerous squamous intraepithelial lesions, typically classified as low and high grade according to the Bethesda system [8].

Although HPV infection is the main risk factor for CC, the infection alone is often an insufficient event for cancer development [8]. HPV can be detected in women with normal cytology and not every infected woman will present lesions in the cervix and evolve to cancer [9]. Many factors are associated with the HPV infection. Among them, studies cite the early onset of sexual activity, ethnicity, use of contraceptives,

Responsible Editor: Luis Augusto Nero

✉ Léia Carolina Lucio
leiacarol@gmail.com

[1] Universidade Estadual Do Oeste Do Paraná, Programa de Pós-Graduação Em Ciências Aplicadas À Saúde, Francisco Beltrão, Paraná, Brazil

[2] Universidade Estadual Do Oeste Do Paraná, Centro de Ciências da Saúde, Francisco Beltrão, Paraná, Brazil

exposure to tobacco, immunological and genetic factors, coinfection by more than one viral subtype, and oxidative stress that may interfere with viral biology and disease progression [10–14].

A study conducted with adolescents showed that, in addition to smoking, passive exposure to tobacco increased the chances of HPV infection threefold in comparison to individuals not exposed to tobacco [15] (DU et al., 2020). Moreover, both Oh et al. [16] and Seo et al. [17] found that women exposed to secondhand smoke have increased likelihood of high-risk HPV persistence, especially when combined with alcohol consumption. According to Malacco et al. [18], alcohol is an important immunomodulator that can increase susceptibility to chronic diseases, including HPV infection. Regarding sexual behaviors, evidence shows that women with history of STIs and whom have had their first sexual intercourse in teenage years have 1.5 and 2.0 more chances to be infected by HPV, respectively [19].

There is a positive association between the number of sexual partners and the risk of HPV infection [20–23]. As pointed out by Winer et al. [24], the chances for HPV infection increase 25% for each new sexual partner. Not only new sexual partnerships but multiple and simultaneous partnerships are associated with increased chances of HPV infection (OR = 6.38) [25], including more serious subtypes (OR = 2.81) [26].

According to a multicenter study, the prevalence of the virus in Brazil ranges from 13.7 to 54.3%, depending on the population, geographical location, and other factors [27]. A recent study showed 25.41% as the mean prevalence in the national territory [9]. A multicenter study conducted between 2016 and 2017 detected 49.7% as the prevalence for HPV infection in women and men aged 16 to 25 years in the south of the country, the lowest prevalence among the regions evaluated; the same study reported a significant prevalence of HPV, ranging from 10.4 to 24.5%, in women without any alteration in the cervix [11].

Due to the importance of the theme for public and women's health, the present study aimed to determine the prevalence of HPV and investigate factors associated with the infection in women in the city of Francisco Beltrão, southwest of the state of Paraná. The expectation with the results is to outline a general profile of the group with viral infection, thus contributing in the development of prevention strategies for STI, minimizing the pathological evolution of HPV infection.

Methods

Study population and ethics committee

This cross-sectional study included 324 women, aged between 18 and 65 years, who were attending public health services for routine gynecological consultation in the city of Francisco Beltrão, Paraná, Brazil. These services included Family Health Strategy (ESF) of Antonio de Paiva Cantelmo neighborhood; the Basic Health Unit (UBS) located in Cristo Rei, Industrial, and Pinheirinho neighborhoods; and a reference unit for outpatient gynecology and obstetrics care (Instituto da Mulher), located at the Cango neighborhood. The main inclusion criterion was to have had the first sexual intercourse. Pregnant women were excluded. The project was approved by the Ethics Committee in Human Research of Universidade Estadual do Paraná and the National Committee on Ethics in Research, with legal opinion number 2.254.450 and CAAE: 72,983,817.5.0000.0107. After receiving information about the research, those who agreed to participate signed the informed consent form.

Procedures

To characterize the population and to evaluate potential factors associated with HPV infection, the participants were interviewed with the aid of a structured questionnaire. Socioeconomic (age, schooling, marital status, ethnicity, and income), life habits (tobacco consumption and alcoholic beverage), and sexual and gynecological behavior (age of first sexual intercourse, number of sexual partners in life, pregnancy, contraceptive method, past and recent gynecological and vaginal infection, result of the last and current Pap test, immunization) were obtained with this instrument [28]. Subsequently, each participant went through the gynecological consultation with a specialized physician, where the material was collected for the Pap smear. The endocervical brush used in the procedure was preserved and packaged in a tube (Falcon type) with 2 ml of saline solution and kept in a freezer at − 20 °C until molecular analysis for viral detection. Storage of biological material, extraction of genetic material, and detection of HPV were processed in the Molecular Biology and Genetics Laboratory of Unioeste campus Francisco Beltrão. The results of the cytological analysis were provided by the public health services, following the Bethesda classification system (2001).

Molecular analysis

The total genetic material of the participants was isolated using a 200-µl aliquot from the original sample, following the protocol of extraction and purification of nucleic acids "Biological Fluid/blood Genomic DNA extraction kit" – "Purelink® Genomic DNA Mini Kit" (Invitrogen by Thermo Fisher Scientific, Carlsbad, California) according to the manufacturer's instructions and stored at − 20 °C. For HPV detection, a polymerase chain reaction (PCR) technique was performed. The specific primers used for in vitro synthesis of a 450-bp fragment of the coding region of the virus L1 gene were

MY09 (5′-CGTCCMAARGGAWACTGATC-3′) and MY11 (5′-GCMCAGGWCATAAYAATGG-3′). The final volume of each PCR reaction was 25 µl, containing, 10 mm Tris–HCl, 2 mm $MgCl_2$, 0.1 mM dNTPs, 0.5 µm of each primer, and 1.25 U of Taq DNA polymerase (Ludwig Biotechnology Taq DNA Polymerase, Brazil), adding at the end 3.5 µl of the total DNA (50 ng/µl). To determine the quality of the extraction, all samples had a 268-bp segment of the human β-globin gene synthesized from primers GH20 (5′-GAAGCAGGAGGG TAC-3′) and PCO4 (5′-CAACTTCATCCTTCACCC-3′). The amplifications of both genomes were processed in applied Biosystems Veriti Thermal Cycler™ (ThermoFisher Scientific, Germany), following these steps: 10 min at 94 °C, followed by 37 cycles of 1 min at 94 °C; 1 min at 55 °C and 1 min at 72 °C; ending with extension for 10 min at 72 °C [29]. A sample of known genetic material from HeLLa cells, containing the HPV 16 genome, was included as positive control of viral detection.

All amplicons were fractioned by electrophoresis on agarose gel 2%, stained with ethidium bromide, under a potential difference of 150 V for 1 h, visualized under ultra-violet (UV) light, and photo documented.

Statistical analysis

The data were processed in the Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables had the normal distribution verified by the Kolmogorov–Smirnov test. The chi-square test (χ^2), with Yates continuity correction, and Fisher's exact test were used for comparisons between independent categorical variables and HPV infection. As effect size of bivariate analyses, Cramer's *V* was used with the following classifications: weak effect > 0.05, moderate effect > 0.10, strong effect > 0.15, very strong effect > 0.25.

The independent variables with *p*-values < 0.20 in the bivariate analysis were included in the multivariate model of logistic regression, using the stepwise method. The results included odds ratios (OR) with robust standardized errors and 95% confidence intervals via bias-corrected and accelerated (BCa) bootstrap interval calculated with bootstrapping (1000 resamples). To select the best explanatory model of logistic regression, the Hosmer and Lemeshow test was employed (cut-off point > 0.05), together with the Omnibus test of model coefficients (cut-off point < 0.05). Moreover, a lower value of the Akaike information criterion (AIC) and increased of explained variance (R^2 of Nagelkerke) were considered in the choice of the final multivariate model.

Results

The sociodemographic, gynecological, sexual, and life-related characteristics of the participants are presented in Table 1. The prevalence of HPV infection was 6.8%, that is, 22 out of the 324 women. Considering this study's preliminary results, ethnicity and income were associated with HPV infection, with moderate effect size (according to Cramer's *V*; Table 1). Smoking and alcohol consumption also were associated with STIs, although with weak effects. The number of sexual partners in life and new partners in the last year ($p = 0.152$ and 0.080, respectively) was the sexual behavior variables included in the analyses, with a moderate effect size for the latter. The same condition applies to gynecological variables, current cervical alterations ($p < 0.001$), recent vaginal infection ($p = 0.029$), and time of the last Papanicolaou exam ($p = 0.149$); among them, the first one presented the strongest effect for HPV infection, and the other two demonstrated moderate effect size (Table 1).

Logistic regression analyses showed that that the presence of current cervical alterations can increase the chances of having HPV by almost 33 times (OR_{adj}: 32.688; 95%CI: 8.508–125.589; $p < 0.001$). The presence of recent vaginal infection increased the chances of HPV infection by 2.7 times (OR_{adj}: 2.773; 95%CI: 1.048–7.341; $p = 0.040$). The non-white ethnicity increased three times the odds of HPV infection (OR_{adj}: 3.058; 95%CI: 1.056–8.857; $p = 0.039$) (Table 2).

Discussion

The present study found a prevalence of HPV infection of 6.8%. The main factors associated with the infection included the presence of current cervical alterations, recent vaginal infection, and non-white ethnicity. Evidence shows that the prevalence of HPV infection is higher in African and South American countries compared to other regions of the world [3]. However, generalizations should be avoided. For instance, in Ethiopia, a study showed that the prevalence of HPV in specific high-risk subtypes was relatively low in women (7.12%), being even lower among those living with HIV (3%) [19].

When comparing the prevalence of HPV infection found in this study with other locations, it was also possible to find a lower prevalence than those reported for the same age group in South America, including countries such as Chile, Paraguay, Bolivia, and Brazil (18.1%) [3]. Moreover, at a regional level, studies carried out in other cities from the same state found mixed results. For example, a prevalence of 2.2% was reported in the city of Ubiratã, whereas higher rates were found in Maringá (33.8%) and in Curitiba (48%) [30–32].

When comparing data with investigations carried out in southern Brazil, especially in municipalities with similar characteristics to Francisco Beltrão, variations on HPV prevalence were also found. In Cruz Alta (Rio Grande do Sul), the HPV prevalence was 34%, affecting around 15.7%

Table 1 Sociodemographic characteristics, life habits, and gynecological and sexual characteristics with effect for HPV infection in a group of women in southwest Paraná, Brazil

Variables	HPV detection		Effect size*	*p*-value
	Positive ($n=22$)	Negative ($n=302$)		
Socioeconomic/demographic				
Age				
≤ 37 years	10 (45.5%)	126 (41.7%)	0.019	0.732[a]
> 37 years	12 (54.5%)	176 (58.3%)		
Education				
≤ 8 years	10 (45.5%)	98 (32.5%)	0.069	0.212[b]
> 8 years	12 (55.5%)	204 (67.5%)		
Marital status				
Married/common law marriage	13 (59.1%)	218 (72.2%)	0.073	0.286[b]
Single/divorced/widow	9 (40.9%)	84 (27.8%)		
Ethnicity				
White	15 (68.2%)	254 (84.1%)	0.107	**0.104[b]**
Others	7 (31.8%)	48 (15.9%)		
Income (USD)**				
≤ 395.6	17 (77.3%)	168 (56.0%)	0.108	**0.072[c]**
> 395.6	5 (22.7%)	133 (44.0%)		
Life habits				
Smoking				
Yes and former smoker	8 (36.4%)	66 (21.9%)	0.087	**0.193[b]**
No	14 (63.6%)	236 (78.1%)		
Alcohol consumption				
Yes	14 (63.6%)	139 (46.0%)	0.089	**0.169[b]**
No	8 (36.4)	163 (54.0%)		
Sexual/gynecological				
Beginning of sexual intercourse				
≤ 18 years	14 (63.6%)	212 (70.2%)	0.036	0.684[b]
> 18 years	8 (36.4%)	90 (29.8%)		
Continuation				
No. of sexual partners in life				
Up to two partners	8 (36.4%)	165 (54.6%)	0.092	**0.151[b]**
Three or more	14 (63.6%)	137 (45.4%)		
No. new partners last year				
None	14 (63.6%)	246 (81.5%)	0.113	**0.080[b]**
At least one	8 (36.4%)	56 (18.5%)		
Practice of oral sex				
Yes	9 (40.9%)	119 (39.4%)	0.008	1.000[b]
No	13 (59.1%)	183 (60.6%)		
Pregnancy				
No children	7 (31.8%)	59 (19.5%)	0.077	0.268[b]
One or more	15 (68.2%)	243 (80.5%)		
Use of contraceptive				
Used	18 (81.8%)	237 (78.5%)	0.021	1.000[c]
Did not use	4 (18.2%)	65 (20.5%)		
Use of condom				
Yes	5 (22.7%)	44 (14.6%)	0.057	0.350[c]
No	17 (77.3%)	258 (85.4%)		
STI history				
Yes	3 (13.6%)	26 (8.6%)	0.044	0.431[c]
No	19 (86.4%)	276 (91.4%)		

Table 1 (continued)

Variables	HPV detection		Effect size*	*p*-value
	Positive ($n=22$)	Negative ($n=302$)		
Current cervical alterations				
Yes	7 (68.2%)	5 (1.7%)	0.402	**< 0.001**[c]
No	15 (31.8%)	297 (98.3%)		
Recent vaginal infection				
Yes	12 (54.5%)	96 (31.8%)	0.121	**0.029**[a]
No	10 (45.4%)	206 (68.2%)		
Result of previous Pap test				
Normal	14 (63.6%)	202 (66.9%)	0.017	0.938[b]
With alterations	8 (36.4%)	100 (33.1%)		
Time last Pap test				
Up to one year	12 (54.5%)	184 (60.9%)	0.116	**0.149**[c]
More than two years	7 (31.9%)	106 (35.1%)		
Never did	3 (13.6%)	12 (3.4%)		
Doses of vaccine				
None	19 (86.4%)	283 (93.7%)	0.073	**0.180**[c]
At least one of the doses	3 (13.6%)	19 (6.3%)		

*Cramer's *V* value; **one USD = R$ 5.27, 02/02/2022; *[a]Pearson's chi-square; [b]chi-square with Yates continuity correction; [c]Fisher's exact test. In bold, associations that followed for multivariate analysis with $p < 0.20$. *HPV*, human papillomavirus; *STI*, sexually transmitted infection.

Table 2 Multivariate analysis of factors associated with HPV infection in the group of women investigated

Variables	OR_{ajd} (95%CI)	*p*-value
Current cervical alterations		
No	1 (reference)	
Yes	32.688 (8.508–125.589)	< 0.001
Recent vaginal infection		
No	1 (reference)	
Yes	2.773 (1.048–7.341)	0.040
Ethnicity		
White	1 (reference)	
Others	3.058 (1.056–8.857)	0.039

CI, confidence interval; OR_{ajd}, adjusted odds ratio obtained from logistic regression. R^2 Nagelkerke= 24.2%

women [1, 32]. In the city of Rio Grande (Rio Grande do Sul), data from 335 cervical smears indicated that HPV was detected in 24% of the samples [33]. Many factors can explain these variations, such as methodological, cultural, and sociodemographic differences.

Reinforcing the findings of this study, the prevalence of STIs was 6.7% in the municipality of Paiçandu, which is almost identical to what was found in the present study (6.8%), being equally similar to data from North American, European, and Asian countries (i.e., 6.2%) [34]. One tentative explanation is that economic development can play a strong role in the low prevalence of STIs [34].

It could be the case that Francisco Beltrão, the city with the seventh highest with human development index (HDI) in the state of Paraná, scoring above (0.774) than the capital (0.749), had lower HPV infection prevalence due to variations in education, health, and socioeconomical factors [35], thus suggesting that smaller cities might provide better access to health services when compared to major cities. Moreover, although the variable income did not remain a factor associated with HPV infection, most women who presented HPV (77.3%) belonged to the lower income group (Table 1). Indeed, poverty is a social determinant associated with women's vulnerability and may influence the adoption of preventive measures against sexually transmitted infections, restricting access to both proper information and health services [36, 37]. However, in the present study, it was hypothesized that the low prevalence of HPV infection (6.8%) may reflect the structure and efficiency of the health care network offered by the city, allowing screenings and follow-ups of gynecological examinations.

Our results showed that only 12 women presented cervical alterations, and out of these, HPV was detected in seven (58.83%). This finding reflects those cervical alterations constitute the main risk factor associated with HPV infection (OR: 32.688) as the virus can cause severe modifications to the cervix epithelium [38, 39]. The International Agency for Research in Cancer states that about 10 to 30% of women with detectable HPV have cytological abnormalities [40]. A study observed cervical abnormalities in 3% ($n=10$) of the women in their study; however, from these only one was not infected by

the virus [32]. Another study found HPV in 49.7% of women with cervical alterations and 18.2% had high-grade lesions [41]. Therefore, the results of the present study reinforce those changes in the cervix have a strong relationship with HPV infection. Although cervical lesions frequently have viral presence as a leading cause, our results might suggest that tissue instability found in the lesions, along with the presence of other pathogens, could lead to cervical inflammation, hence increasing both the susceptibility of infection and persistence of HPV [42, 43]. Kumari et al. [44], in a review study, stated that a loss of the mutual relationship between the cervical microbiota and the host can lead to injuries and higher risks of HPV infection. In this context, the instability caused by parallel infections increased the chance of the presence of the virus in the group by 2.7 times. Vaginal infection, regardless of origin, may cause inflammation and rupture on the cervical epithelium, thus favoring cellular invasion by HPV [45].

Studies demonstrated that recent infections were potential risk factors for both viral and HPV infections, cervical changes, and carcinogenesis [31, 46]. Evidence exists suggesting that women with HIV might show an association between HPV infection and the vaginal microbiota composition; changes in vaginal microbiota, HPV infection, and the occurrence of bacterial vaginosis, especially *Gardnerella*, could cause mucosal damage, hence increasing the chances of viral infection [47, 48].

In addition to cervical alterations and vaginal infection, the multivariate model maintained ethnicity as a predictor of HPV infection. The sample investigated here was composed of women who self-declared as white, a common feature of the region that has strong Italian, German, and Polish background [49]. However, 31.8% of those who presented HPV reported other ethnicities, which revealed a threefold risk for HPV infection when compared with participants that considered themselves white. Racial or ethnic differences have been observed in incidence rates of invasive cervical cancer (up to 29% higher in black, Hispanic, and non-Hispanic women, compared to non-Hispanic and white ethnicities) [50]. Moreover, authors demonstrated a higher prevalence of HPV among the groups of non-Hispanic blacks, followed by Hispanic and non-Hispanic whites [51]. A study conducted with women with low income in the USA showed that Hispanics born in Mexico had a lower frequency of HPV (16%), followed by an increase between non-Hispanic white (29%), Hispanic born in the USA (35%), and non-Hispanic black (39%) [52]. The explanations for differences in HPV prevalence between and ethnic groups are unclear, although sociocultural conditions and genetic factors may be related [52, 53].

Although this study was the first to examine HPV prevalence in women treated in health services located in Francisco Beltrão (reference for health treatments to other localities), providing data to support preventive and interventional actions, some research limitations should be taken into account. For instance, participants' memory lapses are cited when responding to the questionnaires, which might have interfered in the results. The limited number of women with HPV, although a positive result for the population investigated, may have neglected some risk factors for viral STI infection and also caused statistical bias. Therefore, an expansion of the sample is suggested for future studies, as well as the use of longitudinal designs to follow up the population, evaluating the perseverance of HPV infection.

Conclusion

The present study showed a low prevalence of HPV infection (6.8%) among women assisted by the Unified Health System compared to other municipalities in the state of Paraná and in other developed countries (6.2%). In summary, factors that may be linked to HPV infection were cervical alterations, recent vaginal infection, and women's ethnicity. In this sense, the results indicate some warning signs to the service, especially pointing to the need for a better care for ethnic minorities, since their access to routine gynecological follow-up and regular cervical cancer screening may be limited.

Acknowledgements We would like to thank the Municipal Health Department of Francisco Beltrão, Paraná, which provided access to the Basic Health Units where the collections took place. To the Universidade Estadual do Oeste do Paraná that guaranteed access to the Molecular Biology laboratory where the samples were processed.

Author contribution APRB and LCL contributed to the study design, data analysis and interpretation, article writing, and approval of the final version to be published. ICT, VKK, CRP, LEDF, and GWW contributed to the study design, article writing, and approval of the final version to be published.

Declarations

Ethics approval The present study was approved by the Ethics Committee in Human Research of Universidade Estadual do Paraná and the National Committee on Ethics in Research, with legal opinion number 2.254.450 and CAAE: 72983817.5.0000.

Consent to participate Participants provided written informed consent before enrolling in the present study.

Consent for publication Participants signed informed consent regarding publishing obtained data in this study.

Conflict of interest The authors declare no competing interests.

References

1. Coser J, Boeira TR, Wolf JM, Cerbaro K, Simon D, Lunge VR (2016) Cervical human papillomavirus infection and persistence: a

clinic-based study in the countryside from South Brazil. Brazilian J Infect Dis 20:61–68. https://doi.org/10.1016/j.bjid.2015.10.008
2. Tumban E (2019) A current update on human papillomavirus-associated head and neck cancers. Viruses 11:1–19. https://doi.org/10.3390/v11100922
3. Bruni L, Albero G, Serrano B et al (2021) ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human papillomavirus and related diseases in the world. Summary Report 22 October 2021. https://hpvcentre.net/statistics/reports/XWX.pdf. Accessed 2 November 2021
4. Zhu H, He Z, Tian M, Wang D, He J, Xu T (2020) DNA methylation and hydroxymethylation in cervical cancer: diagnosis, prognosis and treatment. Front Genet 11:1–12. https://doi.org/10.3389/FGENE.2020.00347
5. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021) Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71:209–249. https://doi.org/10.3322/caac.21660
6. Secretaria de Estado da Saúde do Paraná (2018) Cenário epidemiológico da neoplasia maligna da mama e do colo do útero em mulheres residentes no Paraná. https://www.saude.pr.gov.br/sites/default/arquivos_restritos/files/documento/2020-04/cenariodepidemiologcandecerdemama.pdf. Acessed 2 November 2021
7. Mac M, Moody CA (2020) Epigenetic regulation of the human papillomavirus life cycle. Pathog (Basel, Switzerland) 9(6):1–18. https://doi.org/10.3390/PATHOGENS9060483
8. Schiffman M, Kjaer SK (2003) Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. J Natl Cancer Inst Monogr 31:14–19. https://doi.org/10.1093/oxfordjournals.jncimonographs.a003476
9. Colpani V, Falcetta FS, Bidinotto AB et al (2020) Prevalence of human papillomavirus (HPV) in Brazil: a systematic review and meta-analysis. PLoS ONE 15:1–34. https://doi.org/10.1371/JOURNAL.PONE.0229154
10. Castellsagué X, Bosch FX, Muñoz N et al (2002) Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med 346:1105–1112. https://doi.org/10.1056/NEJMoa011688
11. Wendland EM, Villa LL, Unger ER et al (2020) Prevalence of HPV infection among sexually active adolescents and young adults in Brazil: the POP-Brazil Study. Sci Rep 10:1–10. https://doi.org/10.1038/s41598-020-61582-2
12. Gadducci A, Barsotti C, Cosio S, Domenici L, Riccardo Genazzani A (2011) Smoking habit, immune suppression, oral contraceptive use, and hormone replacement therapy use and cervical carcinogenesis: a review of the literature. Gynecol Endocrinol 27:597–604. https://doi.org/10.3109/09513590.2011.558953
13. Pudney J, Quayle AJ, Anderson DJ (2005) Immunological microenvironments in the human vagina and cervix: mediators of cellular immunity are concentrated in the cervical transformation zone1. Biol Reprod 73:1253–1263. https://doi.org/10.1095/biolreprod.105.043133
14. Cruz-Gregorio A, Manzo-Merino J, Lizano M (2018) Cellular redox, cancer and human papillomavirus. Virus Res 246:35–45. https://doi.org/10.1016/j.virusres.2018.01.003
15. Du X, Li M, Zhou Y, Yang H, Isachenko V, Takagi T, Meng Y (2020) Evidence of passive smoking as a risk factor of high-grade squamous intraepithelial lesion: a case-control study. Biol Pharm Bull 43:1061–1066. https://doi.org/10.1248/bpb.b19-01098
16. Oh HY, Seo SS, Kim MK et al (2014) Synergistic effect of viral load and alcohol consumption on the risk of persistent high-risk human papillomavirus infection. PLoS ONE 20:e104374. https://doi.org/10.1371/journal.pone.0104374
17. Seo SS, Oh HY, Kim MK, Lee DO, Chung YK, Kim JY, Lee CW (2019) Combined effect of secondhand smoking and alcohol drinking on risk of persistent human papillomavirus infection. Biomed Res Int 21:5829676. https://doi.org/10.1155/2019/5829676
18. Malacco NLSO, Souza JAM, Martins FRB et al (2020) Chronic ethanol consumption compromises neutrophil function in acute pulmonary Aspergillus fumigatus infection. Elife 9:e58855. https://doi.org/10.7554/eLife.58855
19. Temesgen MM, Alemu T, Shiferaw B et al (2021) Prevalence of oncogenic human papillomavirus (HPV 16/18) infection, cervical lesions and its associated factors among women aged 21–49 years in Amhara region. Northern Ethiopia PLoS ONE 16:e0248949. https://doi.org/10.1371/journal.pone.0248949
20. Baseman JG, Koutsky LA (2005) The epidemiology of human papillomavirus infections. J Clin Virol 32:S16-24. https://doi.org/10.1016/j.jcv.2004.12.008
21. González P, Hildesheim A, Rodríguez AC et al (2010) Behavioral/lifestyle and immunologic factors associated with HPV infection among women older than 45 years. Cancer Epidemiol Biomarkers Prev 19:3044–3054. https://doi.org/10.1158/1055-9965
22. Rositch AF, Burke AE, Viscidi RP, Silver MI, Chang K, Gravitt PE (2012) Contributions of recent and past sexual partnerships on incident human papillomavirus detection: acquisition and reactivation in older women. Cancer Res 72:6183–6190. https://doi.org/10.1158/0008-5472
23. Yang J, Wang W, Wang Z et al (2020) Prevalence, genotype distribution and risk factors of cervical HPV infection in Yangqu, China: a population-based survey of 10086 women. Hum Vaccin Immunother 16:1645–1652. https://doi.org/10.1080/21645515.2019.1689743
24. Winer RL, Feng Q, Hughes JP, O'Reilly S, Kiviat NB, Koutsky LA (2008) Risk of female human papillomavirus acquisition associated with first male sex partner. J Infect Dis 197:279–282. https://doi.org/10.1086/524875
25. Ma S, Stern JE, Feng Q, Hughes JP, Hawes SE, Winer RL (2017) Incidence and risk factors for human papillomavirus infections in young female online daters. J Med Virol 89:2029–2036. https://doi.org/10.1002/jmv.24891
26. Winer RL, Hughes JP, Feng Q, Stern JE, Xi LF, Koutsky LA (2016) Incident detection of high-risk human papillomavirus infections in a cohort of high-risk women aged 25–65 years. J Infect Dis 214:665–675. https://doi.org/10.1093/infdis/jiw074
27. Hohenberger GF, Caierão J, Kops NL (2017) Estudo epidemiológico sobre a prevalência nacional de infecção pelo HPV (POP - Brasil): Resultados preliminares. Associação Hospitalar Moinhos de Vento - Porto Alegre, Brasil. http://www.iepmoinhos.com.br/pesquisa/downloads/LIVRO-POP_Brasil_-_Resultados_Preliminares.pdf. Accessed 10 October 2021
28. Oliveira GR, Corrêa Vieira VC, Barra MFM, Soares VDMA, Conçalves CV, Martinez AMB (2013) Fatores de risco e prevalência da infecção pelo HPV em pacientes de Unidades Básicas de Saúde e de um Hospital Universitário do Sul do Brasil. Rev Bras Ginecol Obstet 35:226–232
29. Trugilo KP, Cebinelli GCM, Berti FCB et al (2019) Polymorphisms in the TGFB1 signal peptide influence human papillomavirus infection and development of cervical lesions. Med Microbiol Immunol 208:49–58. https://doi.org/10.1007/s00430-018-0557-y
30. Ribas-Silva RC, Silva DP (2013) Prevalência de mulheres infectadas pelo Papilomavírus humano em Ubiratã-Paraná. SaBios-Revista Saúde e Biol 8:69–76
31. Suehiro TT, Gimenes F, Souza RP et al (2021) High molecular prevalence of HPV and other sexually transmitted infections in a population of asymptomatic women who work or study at a Brazilian university. Rev Inst Med Trop Sao Paulo 63:1–10. https://doi.org/10.1590/S1678-9946202163001

32. Coser J, Boeira TR, Simon D, Kazantzi ASF, Ikuta N, Lunge VR (2013) Prevalence and genotypic diversity of cervical human papillomavirus infection among women from an urban center in Brazil. Genet Mol Res 12:4276–4285. https://doi.org/10.4238/2013.February.19.3
33. Oliveira GR, Vieira VC, Ávila EC et al (2017) Human papillomavirus type distribution and HPV16 intratype diversity in southern Brazil in women with and without cervical lesions. Mem Inst Oswaldo Cruz 112:492–498. https://doi.org/10.1590/0074-02760160530
34. da Silva MC, Martins HP, de Souza JL, Tognim MC, Svidzinski TI, Teixeira JJ, Consolaro ME (2012) Prevalence of HPV infection and genotypes in women with normal cervical cytology in the state of Paraná, Brazil. Arch Gynecol Obstet 286:1015–1022. https://doi.org/10.1007/s00404-012-2399-y
35. Programa das Nações Unidas para o Desenvolvimento, Pesquisa, Índice de Desenvolvimento Humano,| IDH (2021). Instituto Brasileiro de Geografia e Estatística, IBGE. https://cidades.ibge.gov.br/brasil/pr/francisco-beltrao/pesquisa/37/30255?tipo=ranking. Accessed 14 December 2021
36. Henry KA, Stroup AM, Warner EL, Kepka D (2016) Geographic factors and human papillomavirus (HPV) vaccination initiation among adolescent girls in the United States. Cancer Epidemiol Biomarkers Prev 25:309–317. https://doi.org/10.1158/1055-9965.EPI-15-0658
37. Atkinson AE, Matute Mandujano CA, Bejarano S, Kennedy LS, Tsongalis GJ (2019) Screening for human papillomavirus in a low- and middle-income country. J Glob Oncol 5:1–7. https://doi.org/10.1200/JGO.18.00233
38. Singh N, Sobti RC, Suri V et al (2013) Downregulation of tumor suppressor gene PML in uterine cervical carcinogenesis: impact of human papillomavirus infection (HPV). Gynecol Oncol 128:420–426. https://doi.org/10.1016/J.YGYNO.2012.11.041
39. Rizzuto I, Nalam M, Jiang J, Linder A, Rufford B (2018) Risk factors for HPV persistence and cytology anomalies at follow-up after treatment for cervical dysplasia. Int J Gynaecol Obstet 141:240–244. https://doi.org/10.1002/IJGO.12431
40. Working Group on the Evaluation of Carcinogenic Risks to Humans, Biological Agents (2012) Human papillomaviruses. In: International Agency for Research on Cancer (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 100B.), Lyon, France. https://www.ncbi.nlm.nih.gov/books/NBK304347/. Accessed 10 October 2021
41. Melo A, Montenegro S, Liempi S, Moreno S, de La Barra T, Guzmán P et al (2019) Frecuencia de alteraciones citológicas cervicales y virus papiloma humano en una muestra de estudiantes universitarias en Temuco, Chile. Rev Chil Infectol 36:421–427. https://doi.org/10.4067/S0716-10182019000400421
42. Silva J, Cerqueira F, Medeiros R (2014) Chlamydia trachomatis infection: implications for HPV status and cervical cancer. Arch Gynecol Obstet 289:715–723. https://doi.org/10.1007/s00404-013-3122-3
43. Ghosh I, Mandal R, Kundu P, Biswas J (2016) Association of genital infections other than human papillomavirus with pre-invasive and invasive cervical neoplasia. J Clin Diagn Res 10:XE01–XE06. https://doi.org/10.7860/JCDR/2016/15305.7173
44. Kumari S, Bhor VM (2021) Association of cervicovaginal dysbiosis mediated HPV infection with cervical intraepithelial neoplasia. Microb Pathog 152:104780. https://doi.org/10.1016/j.micpath.2021.104780
45. Crothers JW, Mount SL, Harmon M, Wegner E (2015) The utility of human papillomavirus testing in young women with atypical glandular cells on pap test. J Low Genit Tract Dis 19:22–26. https://doi.org/10.1097/LGT.0000000000000044
46. Guidry JT, Scott RS (2017) The interaction between human papillomavirus and other viruses. Virus Res 231:139–147. https://doi.org/10.1016/J.VIRUSRES.2016.11.002
47. Shannon B, Yi TJ, Perusini S et al (2017) Association of HPV infection and clearance with cervicovaginal immunology and the vaginal microbiota. Mucosal Immunol 10:1310–1319. https://doi.org/10.1038/mi.2016.129
48. Zhou Y, Wang L, Pei F et al (2019) Patients with LR-HPV infection have a distinct vaginal microbiota in comparison with healthy controls. Front Cell Infect Microbiol 9:1–11. https://doi.org/10.3389/FCIMB.2019.00294/BIBTEX
49. Chao XP, Sun TT, Wang S, Fan QB, Shi HH, Zhu L, Lang JH (2019) Correlation between the diversity of vaginal microbiota and the risk of high-risk human papillomavirus infection. Int J Gynecol Cancer 29:28–34. https://doi.org/10.1136/IJGC-2018-000032
50. Howlader NNA, Krapcho M, Garshell J et al (2015) SEER Cancer Statistics Review, 1975–2012. Bethesda, MD: National Cancer Institute. https://seer.cancer.gov/archive/csr/1975_2012/Accessed 10 October 2021
51. Hariri S, Unger ER, Powell SE et al (2012) Human papillomavirus genotypes in high-grade cervical lesions in the United States. J Infect Dis 206:1878–1886. https://doi.org/10.1093/INFDIS/JIS627
52. Lin L, Benard VB, Greek A, Hawkins NA, Roland KB, Saraiya M (2015) Racial and ethnic differences in human papillomavirus positivity and risk factors among low-income women in Federally Qualified Health Centers in the United States. Prev Med (Baltim) 81:258–261. https://doi.org/10.1016/J.YPMED.2015.08.027
53. Camara HB, Anyanwu M, Wright E, Kimmitt PT (2018) Human papilloma virus genotype distribution and risk factor analysis amongst reproductive-age women in urban Gambia. J Med Microbiol 67:1645–1654. https://doi.org/10.1099/JMM.0.000848