Research, Society and Development, v. 11, n. 11, e103111133571, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i11.33571

Risk prediction for HPV-induced lesions in early sexual intercourse

Previsão de risco para lesões induzidas por HPV em relações sexuais precoces

Predicción del riesgo de lesiones inducidas por HPV en las relaciones sexuales tempranas

Received: 07/31/2022 | Reviewed: 08/07/2022 | Accept: 08/07/2022 | Published: 08/16/2022

Dayane da Silva Pereira Mullar
ORCID: https://orcid.org/0000-0002-4540-8144
Rio de Janeiro State University, Brazil
E-mail: dayane.meduerj@gmail.com
Ricardo José de Souza
ORCID: https://orcid.org/0000-0003-0815-7136
Rio de Janeiro State University, Brazil
E-mail: rsouzaj@gmail.com
Marco Aurelio Pinho Oliveira
ORCID: https://orcid.org/0000-0001-6159-6299
Rio de Janeiro State University, Brazil
E-mail: endometriose@gmail.com
Leila Cristina Soares
ORCID: https://orcid.org/0000-0001-8360-3189
Rio de Janeiro State University, Brazil
E-mail: lcs1507@yahoo.com.br

Abstract
Objective: This study aims to compare the effects of age at first sexual intercourse (sexarche) and menarche-sexarche interval in predicting the incidence of human papillomavirus (HPV)-induced lesions. *Material & Methods*: This is a cross-sectional study of 698 women with normal or HPV-induced lesions, diagnosed cytologically or histologically. *Results*: After multivariate analysis, the probability of developing HPV-induced lesions increased by 63% for those with menarche-sexarche interval of 3 years or less. Additionally, smoking, parity, and age were relevant in prediciting the risk. *Conclusion*: Sexarche within the first 3 years from menarche was associated with the occurrence of HPV-induced lesions as an independent factor, unlike sexarche, indicating that menarche-sexarche interval of less than 3 years may be an important parameter for the definition of early sexual intercourse.
Keywords: Sexual intercourse; Sexual behavior; Papillomavirus infection; Sexually transmitted infection.

Resumo
Objetivo: Este estudo tem como objetivo comparar os efeitos da idade da primeira relação sexual (sexarca) e do intervalo menarca-sexarca na predição da incidência de lesões induzidas pelo papilomavírus humano (HPV). *Material e Métodos*: Trata-se de um estudo transversal de 698 mulheres com lesões normais ou induzidas pelo HPV, diagnosticadas citológica ou histologicamente. *Resultados*: Após análise multivariada, a probabilidade de desenvolver lesões induzidas pelo HPV aumentou em 63% para aquelas com intervalo menarca-sexarca de 3 anos ou menos. Além disso, tabagismo, paridade e idade foram relevantes na previsão do risco. *Conclusão*: A sexarca nos primeiros 3 anos da menarca foi associada à ocorrência de lesões induzidas pelo HPV como um fator independente, diferentemente da sexarca, indicando que o intervalo menarca-sexarca menor que 3 anos pode ser um parâmetro importante para a definição de sexo precoce relação sexual.
Palavras-chave: Relações sexuais; Comportamento sexual; Infecção por papilomavírus; Infecção sexualmente transmissível.

Resumen
Objetivo: Este estudio pretende comparar los efectos de la edad de la primera relación sexual (sexarquia) y el intervalo menarquia-sexarquia en la predicción de la incidencia de lesiones inducidas por el virus del papiloma humano (VPH). *Material y Métodos*: Se trata de un estudio transversal de 698 mujeres con lesiones normales o inducidas por VPH, diagnosticadas citológica o histológicamente. *Resultados*: Después del análisis multivariado, la probabilidad de desarrollar lesiones inducidas por VPH aumentó en un 63% para aquellas con intervalo menarquia-sexarquia de 3 años o menos. Además, el tabaquismo, la paridad y la edad fueron relevantes para predecir el riesgo. *Conclusión*: La sexarquia dentro de los primeros 3 años desde la menarquia se asoció con la aparición de lesiones inducidas por el VPH como factor independiente, a diferencia de la sexarquia, lo que indica que el intervalo menarquia-sexarquia de menos de 3 años puede ser un parámetro importante para la definición de la sexualidad temprana.
Palabras clave: Relaciones sexuales; Comportamiento sexual; Infección por virus del papiloma; Infección transmitida sexualmente.

1. Introduction

Early age at first sexual intercourse (sexarche) has been associated with an increased risk of human papillomavirus (HPV) infection, which, in susceptible women, is responsible for almost all cases of invasive cervical cancer.(Louie et al., 2009)

The mechanism by which early sexarche contributes to the risk of cervical carcinogenesis can be explained by the influence of steroids on HPV infection and on the host's immune response to HPV during preadolescence and adolescence.(Adhikari et al., 2019)

Precursor lesions can develop as a consequence of persistent HPV infection in a process that lasts from 5 to 10 years.(Amo-Adjei & Tuoyire, 2018) The first HPV infection generally occurs immediately after the first sexual intercourse.(Brinton et al., 1987) Therefore, sexarche is a reasonable reference for the first exposure to HPV.

A precise definition of early sexual intercouse is not found in various studies. Adolescents, pregnant women, and users of hormonal contraceptives get more cervical ectopy, i.e., exposure of the columnar epithelium in the ectocervix, compared to other groups.(Plummer et al., 2012) However, it is not yet clear if the increased risk is more related to time of exposure of the immature metaplasia area to HPV or only to sexarche, considering the increased time to HPV exposure and biological immaturity. This study aims to compare the effects of menarche–sexarche interval and sexarche in predicting the occurrence of precursor lesions.

2. Methodology

A cross-sectional observational study was carried out as described by Setia (Setia,2016), retrospectively analyzing the medical records of women treated at the lower genital tract pathology outpatient clinic of the Pedro Ernesto University Hospital between January 2012 and December 2020. None of the participants had been vaccinated at the time of the data collection. Data collection for this study took place between 2012-2020, and the HPV vaccine became available in Brazil in 2014. That year, the vaccine was made for girls between 11 and 13 years old and in subsequent years, for girls up to 14 years old. Medical records of women referred for low-grade lesions, high-grade lesions, and cancer on cytology or biopsy were included in the study, as well as those referred for benign lesions such as polyps, cervicitis, cervix with irregular appearance, and metaplasia. Only medical records with complete information on all studied variables were considered for this study. Sociodemographic and clinical data were collected.

The study was approved by the Ethics Committee via Plataforma Brasil (CAAE number 41958320.6.0000.5259).

Statistical analysis was performed using the R version 4.0.5 software. Quantitative data were presented as medians and interquartile ranges (IQRs), and qualitative data were presented as *n* or percentages. To observe possible associations between the variables, the chi-square test, Fisher's test, or the Wilcoxon–Mann–Whitney test was used, when pertinent. Multiple logistic regression models were used to assess the effects of predictor variables. Variables were included in the multivariate model when the p value was less than 0.2 in the univariate analysis. Age, smoking, use of hormonal contraceptives, parity, menarche–sexarche interval equal to 3 years or less, and sexarche equal to 16 years or less were treated as independent variables. Statistical significance was defined as $p < 0.05$. Adjusted odds ratio (OR) were calculated with a 95% confidence interval (CI).

3. Results

A total of 1,134 medical records were analyzed, 436 of which were excluded due to incomplete information, leaving 698 medical records.

The median age was 41 years (IQR = 31–51). The median sexarche was 16 years old (IQR = 15–18). The median menarche–sexarche interval was 4 (IQR = 2–6).

In terms of parity, the median was 2 (IQR = 1–3). Moreover, the use of hormonal contraceptives was reported in 112 women (16.1%), and concomitant immunosuppression was observed in 37 women (5.3%).

Five hundred and twenty women (74.5%) declared themselves nonsmokers, 56 (8%) reported smoking in the past (not smoking for a year or more), and 122 (17.5%) declared themselves current smokers.

The main final diagnoses were as follows: benign changes in 288 women (41.3%), low-grade lesion in 110 (15.8%), high-grade lesion in 228 (32.7%), and invasive carcinoma in 72 (10.2%). Low-grade, high-grade, and cancer lesions were considered HPV-induced lesions and analyzed together.

The groups with earlier sexarche were significantly more related to having HPV-induced lesions, except in the group with sexarche earlier than 11 years old, because of the low sample of women in this group (only 5 women) (OR 2.82; 0.27-139.63). The group with sexarche before 12 years old had a wide CI because of the same reason (small sample of women), besides the significant difference (OR 6.17; 1.44–55.47). (Table 1)

Table 1. Menarche–sexarche interval and HPV-induced lesions risk.

	HPV-induced lesions (N,%)	Benign changes (N,%)		HPV-induced lesions (N,%)	Benign changes (N,%)	OR (CI)
Menarche–sexarche interval ≤ 1 year	92 70.2%	39 29.8%	Menarche–sexarche interval >1 year	318 56.1%	249 43.9%	1.84 (1.21-2.86)
Menarche–sexarche interval ≤ 2 years	171 69.5%	75 30.5%	Menarche–sexarche interval >2 years	239 52.9%	213 47.1%	2.03 (1.44-2.86)
Menarche–sexarche interval ≤3 years	176 50.6%	172 49.4%	Menarche–sexarche interval >3 years	124 35.4%	226 64.6%	1.86 (1.36-2.56)
Menarche–sexarche interval ≤ 4 years	287 64.6%	157 35.4%	Menarche–sexarche interval >4 years	123 48.4%	131 51.6%	1.94 (1.40-2.69)
Menarche–sexarche interval ≤ 5 years	321 62.7%	191 37.3%	Intervalo menarca-Sexarche >5 years	89 47.8%	97 52.2%	1.83 (1.29-2.60)
Menarche–sexarche interval ≤ 6 years	350 61.7%	217 38.3%	Menarche–sexarche interval >6 years	60 45.8%	71 54.2%	1.91 (1.28-2.85)
Menarche–sexarche ≤ 7 years	365 60.5%	238 39.5%	Menarche–sexarche interval >7 years	45 47.4%	50 52.6%	1.70 (1.08-2.70)
Menarche–sexarche interval ≤ 8 years	377 (60.2%)	249 (39.8%)	Menarche–sexarche interval >8 years	33 (45.8%)	39 54.2%)	1.79 (1.06-3.02)

OR - odds ratio; CI – confidence interval. Source: Authors.

The groups with shorter menarche–sexarche intervals of up to 12 years were significantly more related to developing HPV-induced lesions. From an interval of 12 years or more, despite remaining significantly longer, the CIs were widened because of the group's quantity. Moreover, they were expressively larger (OR 3.95; 1.45 – 12.5). (Table 2)

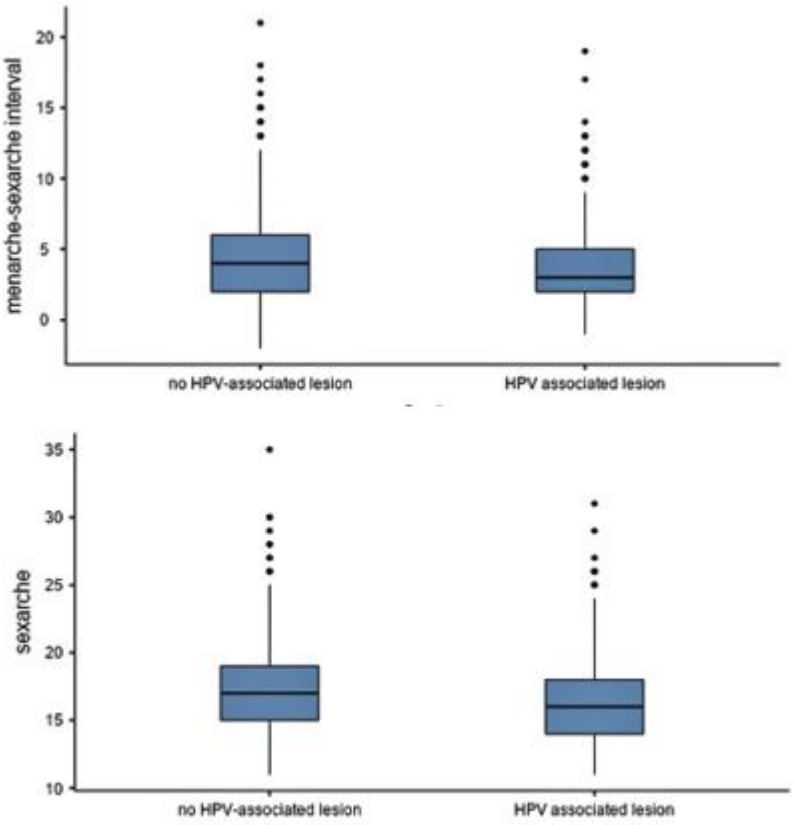
Table 2. Sexarche and HPV-induced lesions risk.

	HPV-induced lesions	Benign changes		HPV-induced lesions	Benign changes	OR (CI)
Sexarche ≤11 years	4 80%	1 20%	Sexarche> 11 years	406 58.6%	287 41.4%	2.82 (0.27-139.63)
Sexarche ≤ 12 years	17 89.5%	2 10.5%	Sexarche> 11 years	393 57.9%	286 42.1%	6.17 (1.44-55.47)
Sexarche ≤ 13 years	49 72%	19 28%	Sexarche> 13 years	371 57%	269 43%	1.92 (1.08-3.54)
Sexarche ≤ 14 years	104 70.7%	43 29.3%	Sexarche> 14 years	306 55.5%	245 45.5%	1.93 (1.29-2.94)
Sexarche ≤ 15 years	186 67.4%	90 32.6%	Sexarche> 15 years	198 46.9%	224 53.1%	1.82 (1.32-2.54)
Sexarche ≤ 16 years	243 66.9%	120 33.1%	Sexarche> 16 years	167 49.9%	168 50.1%	2.03 (1.48-2.80)
Sexarche ≤ 17 years	297 64.6%	163 35.4%	Sexarche> 17 years	113 47.5%	125 52.5%	2.01 (1.45-2.80)
Sexarche ≤ 18years	334 63%	196 37%	Sexarche> 18 years	76 45.2%	92 54.8%	2.06 (1.43-2.98)

OR - odds ratio; CI – confidence interval. Source: Authors.

In women with no HPV-induced lesions, the median sexarche was 17 years old, and the menarche–sexarche interval was 4 years. On the other hand, in those with HPV-induced lesions, the median sexarche was 16 years old, and the menarche–sexarche interval was 3 years. (Figure 1)

Figure 1. Boxplots of menarche-sexarche and sexarche and HPV-associated lesion showing the median, the first quartile and the third quartile.



Source: Authors.

ROC curves of sexarche and menarche–sexarche interval show an area of 0.61 (CI 0.57–0.65 for both sexarche and menarche–sexarche interval. The best cutoff points (with sensitivitiy of 68.75% for sexarche and 73.96% for menarche-sexarche interval) were identified as sexarche of 16 years old or earlier and menarche–sexarche interval of 3 years or less. Thus, these were the cutoff points used for our definition of early sexual intercourse.

In Table 3, it is possible to observe the comparison between the groups with HPV-induced lesions and those with benign changes. Logistic regression showed that only menarche–sexarche interval, use of hormonal contraceptives, and smoking were relevant in predicting risk of developing HPV-induced lesions (Table 3).

Table 3. Comparison between HPV-induced lesions and benign changes (Mann–Whitney test).

	HPV-induced lesions (N=410)	Benign changes (N=288)	Value P	Adjusted OR
Median age (IQR)	38 (30-47)	45 (33-55)	p<0.0001	0.97 (0.96 - 0.99)*
Median Parity (IQR)	2 (1-3)	2 (1-3)	p=0.051	1.13 (1.02 -1.25)*
Smoking			p<0.001	1.32
Current	86 (21%)	36 (12.5%)		(1.07 - 2.66)*
Before	35 (8.5%)	21 (7.3%)		
Non-smoking	289 (70.5%)	231 (80.2%)		
Hormonal Contraceptives				1.56
Yes	79 (19.3%)	33 (11.5%)	p=0.006	(0.99 - 2.51)
No	330 (80.7%)	254 (88.5%)		
Immunossupressive disease				0.82
Yes	20 (4.9%)	17 (5.9%)	p=0.55	(0.42 - 1.61)
No	390 (95.1%)	271 (94.1%)		
Menarche-sexarche interval ≤ 3 years	228	120	p<0.001	1.63 (1.12 - 2.38)*
sexarche≤ 16 years old	232	111	p<0.001	1.07 (0.71 - 1.60)

IQR - interquartile range; * statistical significance. Source: Authors.

The result of logistic regression showed that, for menarche–sexarche interval equal to 3 years or less, the chance of HPV-induced lesion increased by 63%. Moreover, smoking and parity also proved to be significant. In contrast, increasing age was considered a protective factor. Sexarche and use of contraceptives, after correction, were not significant.

4. Discussion

The natural history of cervical carcinogenesis includes the acquisition of a high-risk HPV, its persistence, the development of precancerous lesions, and eventually the progression to invasion. (Adebamowo et al., 2022; Sichero et al., 2020) HPV is a necessary but not sufficient factor, therefore, other biological, behavioral and environmental cofactors have been implicated in the development of cancer.(Kops et al., 2019)

Among the risk factors for cervical cancer, sexual behaviors related to HPV infection, such as early sexual intercourse and the multiplicity of partners, stand out. (Pereira Filho et al., 2021) Risky behaviors such as inconsistent use use of contraceptives in sexual intercourses, multiple sexual partners and drug-use has been associated with early sexual intercourse. (Roman Lay et al., 2021)

Adolescents with early sexarche are more at risk for sexual and reproductive health problems, such as abortion, sexually transmitted infections, sexual abuse, and unplanned pregnancy.(Yaya & Bishwajit, 2018) Considering that sexual behavior determines HPV exposure, sexarche is extremely significant in the development of cervical cancer precursor lesions. Cervical cancer precursor lesions were once associated with high-risk sexual behaviors such as unprotected sex and having multiple sexual partners.(Adhikari et al., 2019)

There is controversy on the increased risk of developing high-grade lesions and cervical cancer in women with early sexarche, and the definition of early sexual initiation varies among many studies.(Adhikari et al., 2019; Louie et al., 2009)

Xavier-Junior et al, in a study with 898,921 women, observed that sexarche under 17 years old was a risk factor for the development of high-grade squamous intraepithelial lesion (HSIL) and that women whose sexarche was between 13 and 16 years old had higher prevalence ratios for atypical squamous cells, low-grade squamous intraepithelial lesion, and HSIL.(Xavier-Júnior et al., 2017) Amo-Adjei and Tuoyire observed that sexual initiation before the age of 18 is a strong risk factor for cervical cancer. (Amo-Adjei & Tuoyire, 2018) Likewise, Thakur et al. concluded, in their study of 226 women, that marriage before 18 years old brings an almost threefold higher risk of cervical cancer compared to marriage after 18 years of age.(Thakur et al., 2015) Similar outcomes were also observed by Brinton et al. (Brinton et al., 1987)

Considering the analysis of several ages of sexarche, the results of this study reveal that groups with sexarche before 18 years old are more susceptible to HPV-induced lesions in comparison with groups in which sexarche was after 18 years old. After establishing the cutoff point for early sexarche as 16 years old, based on median sexarche in women with HPV-induced lesions and on analysis of sensitivity and specificity of ROC curve in this study, a woman's first sexual intercourse occurring before 16 years old was considered early.

Ruiz et al. emphasized menarche–sexarche interval as a risk factor for cytological changes and high-grade cervical diseases. (Ruiz et al., 2012) In contrast, Adhikari et al. did not find increased risk of HPV-induced lesions with short intervals between menarche and sexarche.(Adhikari et al., 2019) Both studies considered menarche–sexarche interval of 3 years or less.

Increased vulnerability of adolescents to cervical disease is frequently related to risky behaviors, but biological differences in immune function of the cervical mucosa can also contribute.(Hwang et al., 2011) Biological immaturity might be responsible for susceptibility to HPV infections and its association with sexarche.(Louie et al., 2009) Moreover, squamous metaplasia of the cervix, a physiological process that occurs mainly at the beginning of puberty, could explain the need to associate sexarche with menarche.(Doorbar & Griffin, 2019) The area of metaplasia, called the transformation zone, has been recognized as the site where HPV infection tends to cause cancer, and it is believed that the susceptibility of this area is related to the denudation of the stratified epithelium, facilitating the exposure of the layer.(Louie et al., 2009) In theory, an active metaplastic scenario is the ideal condition for HPV infections because the virus requires differentiation and replication of the host cell for its own replication and survival.(Hwang et al., 2011; Soares et al., 2019) In addition, earlier sexual initiation implies a longer period of sexual activity. (Mekuria et al., 2021)

After testing menarche–sexarche intervals of up to 12 years, the results showed that the groups with the shortest intervals are more susceptible to HPV-induced lesions. The median of the intervals was 3 years, and the ROC curve also described that same interval as the factor of greatest sensibility regarding the specificity function. As a result, this study considers 3 years for the menarche–sexarche interval as the cutoff point to define early sexual activities.

The main evidence on the relevance of metaplasia in cancer and precursor lesions is that high-risk HPV infects several epithelium areas but causes cancer with a distinct frequency. Thus, there are only 20,000 cases of vaginal or vulvar cancer per year and 13,000 cases of penile cancer per year throughout the world, while there are 53,000 cases of cervical cancer per year worldwide.(Doorbar & Griffin, 2019)

Our results also showed a higher prevalence of smoking, in addition to higher parity and younger age, in the group of women with HPV-induced lesions. Hormonal contraceptives and the presence of immunosuppressive diseases did not show a significant association after correction.

However, it is known that hormonal contraception is associated with an increased risk of cervical cancer and HPV infection. Considering that the cervical epithelium changes during adolescence and young adulthood, the possible links among hormonal contraceptives, smoking, and maturational activities may influence vulnerability to HPV and other sexually transmitted infections.(Hwang et al., 2009)

After correction of multivariate analysis, the effects of menarche–sexarche interval less than or equal to 3 years remained significant. However, first sexual intercourse at the age of 16 years old or younger was not significant as an independent factor, suggesting that menarche–sexarche interval is more related to occurrence of HPV-induced diseases.

Although early sexual intercourse is considered a risk factor for HPV-induced lesions, the definition of sexual precocity remains imprecise. This work seeks to define the age for early sexarche, showing that this definition may vary depending on age of menarche.

This work has strengths and limitations. Strengths include the analysis of a large sample of patients and the evaluation of several intervals in the histological and cytological diagnoses. Limitations include the retrospective characteristic of the study, which can compromise the accuracy of the data, and the fact that most of the results determined as normal were not submitted for biopsy. However, when biopsies were not performed, the results were only considered normal after two consecutive normal cytologic tests with an interval of six months.

5. Conclusion

After correction with other risk factors, the link between first sexual intercourse before 16 years old and HPV-induced lesions was not significant. Nonetheless, menarche–sexarche interval of 3 years or less was consistently associated with an increase in HPV-induced lesions, indicating that sexual intercourse on the first 3 years after menarche may be an important factor in predicting the occurrence of HPV-induced lesions and may be the best parameter for the definition of early sexual activity. Other studies analyzing sexarche and menarche-sexarche interval parameters would be useful to corroborate these results.

References

Adebamowo, S. N., Befano, B., Cheung, L. C., Rodriguez, A. C., Demarco, M., Rydzak, G., Chen, X., Porras, C., Herrero, R., Kim, J. J., Castle, P. E., Wentzensen, N., Kreimer, A. R., Schiffman, M., & Campos, N. G. (2022). Different human papillomavirus types share early natural history transitions in immunocompetent women. *International Journal of Cancer. Journal International Du Cancer*, *151*(6), 920–929.

Adhikari, I., Eriksson, T., Luostarinen, T., Apter, D., & Lehtinen, M. (2019). Is the risk of cervical atypia associated with the interval between menarche and the start of sexual activity? A population-based cohort study. *BMJ Open*, *9*(9), e030091.

Amo-Adjei, J., & Tuoyire, D. A. (2018). Timing Of Sexual Debut Among Unmarried Youths Aged 15-24 Years In Sub-Saharan Africa. *Journal of Biosocial Science*, *50*(2), 161–177.

Brinton, L. A., Hamman, R. F., Huggins, G. R., Lehman, H. F., Levine, R. S., Mallin, K., & Fraumeni, J. F., Jr. (1987). Sexual and reproductive risk factors for invasive squamous cell cervical cancer. *Journal of the National Cancer Institute*, *79*(1), 23–30.

Doorbar, J., & Griffin, H. (2019). Refining our understanding of cervical neoplasia and its cellular origins. *Papillomavirus Research (Amsterdam, Netherlands)*, *7*, 176–179.

Hwang, L. Y., Ma, Y., Benningfield, S. M., Clayton, L., Hanson, E. N., Jay, J., Jonte, J., Godwin de Medina, C., & Moscicki, A.-B. (2009). Factors that influence the rate of epithelial maturation in the cervix in healthy young women. *The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine*, *44*(2), 103–110.

Hwang, L. Y., Scott, M. E., Ma, Y., & Moscicki, A.-B. (2011). Higher levels of cervicovaginal inflammatory and regulatory cytokines and chemokines in healthy young women with immature cervical epithelium. *Journal of Reproductive Immunology*, *88*(1), 66–71.

Kops, N. L., Bessel, M., Horvath, J. D. C., Domingues, C., de Souza, F. M. A., Benzaken, A. S., Mendes Pereira, G. F., Maranhão, A. G. K., Villa, L. L., Mello, B., & Wendland, E. M. (2019). Factors associated with HPV and other self-reported STI coinfections among sexually active Brazilian young adults: cross-sectional nationwide study. *BMJ Open*, *9*(6), e027438.

Louie, K. S., de Sanjose, S., Diaz, M., Castellsagué, X., Herrero, R., Meijer, C. J., Shah, K., Franceschi, S., Muñoz, N., Bosch, F. X., & International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. (2009). Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries. *British Journal of Cancer*, *100*(7), 1191–1197.

Mekuria, M., Edosa, K., Endashaw, M., Bala, E. T., Chaka, E. E., Deriba, B. S., & Tesfa, B. (2021). Prevalence of Cervical Cancer and Associated Factors Among Women Attended Cervical Cancer Screening Center at Gahandi Memorial Hospital, Ethiopia. *Cancer Informatics*, *20*, 11769351211068431.

Pereira Filho, J. L., Azevedo, G. C. A., Theodoro, T. F., Bonfim, B. F., Monteiro, P. de M., Arouche, R., Anunciação, R. K. L., Pereira, C. L., Buna, S. dos S. S., Silva, Á. L. S. da, Araújo, Á. W. M. da S., Lima, L. A., Arruda, A. C. P., Santos, T. dos, Silva, A. Z., Abreu, I. C., & Silva, S. do N. (2021). Câncer do colo

do útero: Análise epidemiológica e citopatológica no Município de São Luís, Estado do Maranhão, Brasil. *Research, Society and Development*, *10*(8), e33010817074.

Plummer, M., Peto, J., Franceschi, S., & International Collaboration of Epidemiological Studies of Cervical Cancer. (2012). Time since first sexual intercourse and the risk of cervical cancer. *International Journal of Cancer. Journal International Du Cancer*, *130*(11), 2638–2644.

Roman Lay, A. A., Fujimori, E., Simões Duarte, L., & Vilela Borges, A. L. (2021). Prevalence and correlates of early sexual initiation among Brazilian adolescents. *PloS One*, *16*(12), e0260815.

Ruiz, Á. M., Ruiz, J. E., Gavilanes, A. V., Eriksson, T., Lehtinen, M., Pérez, G., Sings, H. L., James, M. K., Haupt, R. M., & FUTURE I and II Study Group. (2012). Proximity of first sexual intercourse to menarche and risk of high-grade cervical disease. *The Journal of Infectious Diseases*, *206*(12), 1887–1896.

Setia, M. S. (2016). Methodology Series Module 3: Cross-sectional Studies. *Indian Journal of Dermatology*, *61*(3), 261–264.

Sichero, L., Picconi, M. A., & Villa, L. L. (2020). The contribution of Latin American research to HPV epidemiology and natural history knowledge. *Brazilian Journal of Medical and Biological Research = Revista Brasileira de Pesquisas Medicas E Biologicas / Sociedade Brasileira de Biofisica ... [et Al.]*, *53*(2), e9560.

Soares, L. C., Braz, F. L. T. A., Araújo, A. R., & Oliveira, M. A. P. (2019). Association of Sexually Transmitted Diseases With Cervical Ectopy: A Systematic Review. *Sexually Transmitted Diseases*, *46*(7), 452–457.

Thakur, A., Gupta, B., Gupta, A., & Chauhan, R. (2015). Risk factors for cancer cervix among rural women of a hilly state: a case-control study. *Indian Journal of Public Health*, *59*(1), 45–48.

Xavier-Júnior, J. C. C., Dufloth, R. M., Vale, D. B., Lima, M. T. de, & Zeferino, L. C. (2017). Early Age at First Sexual Intercourse is Associated with Higher Prevalence of High-grade Squamous Intraepithelial Lesions (HSIL). *Revista Brasileira de Ginecologia E Obstetricia: Revista Da Federacao Brasileira Das Sociedades de Ginecologia E Obstetricia*, *39*(2), 80–85.

Yaya, S., & Bishwajit, G. (2018). Age at First Sexual Intercourse and Multiple Sexual Partnerships Among Women in Nigeria: A Cross-Sectional Analysis. *Frontiers of Medicine*, *5*, 171.