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Age-Specific HPV Prevalence and Risk Factors in Women from a Northeast Area of Brazil - Comparative Study

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Abstract

The objective was to compare the prevalence of HPV infection, lifestyle, and sexual risk behaviors in women at different reproductive stages. Participants were stratified into three groups: fertile age, climacteric, and postmenopausal. After a socio-demographic questionnaire and oncotic cytology examination, a cervical smear was used to detect and genotype HPV using nested PCR and automated sequencing. The postmenopausal group comprised 102 women with a median age of 56.53±8.09 years. They had higher income but fewer years of education, a higher chance of being smokers, and a higher number of pregnancies and children ($P<0.05$). Most participants did not use contraceptives, including condoms ($P <0.05$). Incidence of high-risk HPV was high in non-menopausal women as well as the presence of Gardnerella vaginal infection ($P < 0.05$). Women in all reproductive cycles are subject to HPV infection, however, with some differences regarding the viral type.

Keywords: Menopause, Public Health, Cervical Screening, Human Papillomavirus

1. Introduction

Human papillomavirus (HPV) is considered the most common sexually transmitted infection (STI) worldwide. It is strongly associated with anogenital, cervical, and oropharyngeal tumors(Wendland et al., 2021). The tumorigenic process of cervical cancer caused by HPV infection is usually slow after infection toward the appearance of a lesion and the actual formation of the malignant tumor(Alizon et al., 2017; Kombe Kombe et al., 2021). The prevalence of HPV infection in women has a bipolar pattern(Alizon et al., 2017; de Sanjosé et al., 2007). While the first peak is described by infection occurring at the beginning of a woman's sexual life, the second peak occurs in the climacteric and postmenopausal phases. Alterations in the immune system due to aging may lead to the reactivation of a previous HPV infection, and/or a change in sexual partner and acquired risky behaviors may predispose to acquiring a new HPV infection(Andersen et al., 2019; Lynge et al., 2017). São Luís is a Brazilian city located in the poorest region of Brazil (IBGE, 2010)with the highest incidence rate for new cases of cervical cancer for the year 2020(INCA, 2019).

Considering the high rates of cervical cancer in the state of Maranhão, the second peak of HPV infection, and the increase in life expectancy, elderly women are identified as a group for whom cervical screening strategies should be monitored. This study aimed to compare the prevalence of human papillomavirus infection, lifestyle, and sexual risk behaviors in a sample of women at different reproductive stages in São Luís, Brazil. The results obtained can be used to improve available health regimes and thereby undertake appropriate therapeutic measures.

2. Material and Methods

2.1. Study and Participants

This was an observational, analytical, cross-sectional study carried out in Basic Health Units in São Luís City, Brazil. This study included 353 women recruited by convenience sampling between March 2018 and March

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2019. During routine gynecological consultations, women were invited to participate in the research and, if accepted, informed consent was obtained from all subjects. The inclusion criteria were women over 18 years of age and had sexual activity. Non-inclusion and exclusion criteria included women previously treated for cervical pathology, those using vaginal medication three days before the consultation, either pregnant or postpartum, and those undergoing hysterectomy.

Participants were categorized into three groups: fertile, climacteric, and postmenopausal. The fertile age group comprised participants aged between 18 and 39 years, while the climacteric group comprised participants aged 40 years to those who still menstruated. The postmenopausal group was composed of women who had not menstruated for at least 1 year (self-report). All women participating in the study answered a questionnaire to obtain socio-demographic characteristics and possible risk factors for HPV infection.

2.2. Oncotic Cytology Examination and Collection of Biological Material

The participants underwent an oncotic cytology examination to detect cellular changes in the cervix. Cytological smears were obtained using an Ayres spatula (ectocervical sample) and endocervical brush (endocervical sample), extended on a glass slide, fixed with ethanol, and stained using the Papanicolaou technique. The results were reported using the 2001 Bethesda Reporting System.

Microbiological findings of *Candida* sp., *Trichomonas vaginalis, Gardnerella vaginalis, Lactobacillus* sp., cocci, and other bacilli were also identified through cytological analysis. A cervical swab was collected from the endocervix region with an hc2 DNA Collection sterile brush (QIAGEN, CA, USA) for HPV molecular detection. Samples were stored at −20 °C until processing.

2.3. HPV Detection and Genotyping

DNA was extracted using the QIAamp DNA Mini and Blood Kit (QIAGEN, CA, USA) according to the manufacturer's instructions. DNA concentration was determined using a NanoDrop spectrophotometer (Thermo Fisher Scientific, MA, USA).

HPV detection was performed by amplification using nested PCR with the primer pairs PGMY 09/11 and GP 5 +/6 +(Gravitt et al., 2000). Amplified products were observed by electrophoresis with a 1.5% agarose gel.

HPV-positive samples were submitted to automated sequencing performed by ACTGene Análises Moleculares, which currently provides DNA sequencing services, using an AB 3500 platform (Thermo Fisher Scientific, MA, USA).

To identify the HPV type, nucleotide sequences of the sequenced samples were compared and submitted to the World Nucleotide Database using the BLAST program.

2.4. Statistical analysis

A descriptive statistical analysis was performed on 353 female patients stratified by reproductive age (fertile age, climacteric, and menopause) and presented as a proportion (%). Sexual and reproductive characteristics were categorized in each group for HPV risk factors analysis. Chi-square or Fisher's exact test was applied to compare the groups. One-way analysis of variance (ANOVA) mean comparison test was used to analyze the mean age. Statistical significance was set at $P< 0.05$. Multivariate analysis was performed using multinomial logistic regression stratified in blocks. The statistical program used was the IBM SPSS version 24 (IBM SPSS Statistics for Windows, Armonk, NY)

2.5 Ethics Approval

This study was approved by the Ethics Committee on Human Research of the Federal University of Maranhão, protocol number 2.383.604.

3. Results

Of the 353 participants, 186 were included in the fertile age group, 65 in the climacteric group, and 102 in the postmenopausal group. The socio-demographic characteristics of the 353 patients stratified according to reproductive stage are presented in Table 1.

Table 1. The sociodemographic characteristics of the 353 patients were stratified based on their reproductive stages.

Variables	Total N = 353	Fertile Age N = 186	Climacteric N = 65	Postmenopause N = 102
Age* **(Mean and SD)**	39,74 ± 0,73	28,83 ± 6,42	44,63 ± 3,65	56,53 ± 8,09
Skin color				
White	27 (7,6%)	12 (6,5%)	7 (10,8%)	8 (7,8%)
Brown	217 (61,5%)	120 (64,5%)	39 (60%)	58 (56,9%)
Black	100 (28,5%)	49 (26,3%)	17 (26,2%)	34 (33,3%)
other	9 (2,5%)	5 (2,7%)	2 (3,1%)	2 (2%)
Marital status				
Single	181 (51,3%)	95 (51,1%)	40 (61,5%)	46 (45,1%)
With partner	172 (48,7%)	91 (48,9%)	25 (38,5%)	56 (54,9%)
Monthly income*				
No income	75 (21,2%)	52 (28%)	8 (12,3%)	15 (14,7%)
≤1 minimum wage	118 (33,4%)	65 (34,9%)	26 (40%)	27 (26,5%)
>1 minimum wage	160 (45,3%)	69 (37,1%)	31 (47,7%)	60 (58,8%)
Education level*				
Illiterate	9 (2,5%)	2 (1,1%)	0 (0%)	7 (6,9%)
Elementary school complete/incomplete	117 (33,1%)	39 (21%)	23 (35,4%)	55 (53,9%)
Secondary school complete/incomplete	193 (54,7%)	118 (63,4%)	38 (58,5%)	37 (36,3%)
Graduate school complete/incomplete	34 (9,6%)	27 (14,5%)	4 (6,2%)	3 (2,9%)

SD = standard deviation. The mean age was analyzed by ANOVA One-Way Mean Comparison Test. Data in proportion format were evaluated using the chi-square and Fisher's exact tests. *P< 0.05.

The mean age was significantly higher (56.53 ± 8.09 years) in the postmenopausal group (P<0.05). Postmenopausal women had a higher monthly income but fewer years of education than the fertile and climacteric women (P<0.05).

Table 2. The lifestyle and sexual life data of participants were stratified based on the reproductive stage.

Variables	Total N = 353	Fertile Age N = 186	Climacteric N = 65	Postmenopause N = 102
Smoking status*				
No	261 (73,9%)	143 (76,9%)	55 (84,6%)	63 (61,8%)
Yes	92 (26,1%)	43 (23,1%)	10 (15,4%)	39 (38,2%)
Alcohol consumption*				
No	190 (53,8%)	83 (44,6%)	38 (58,5%)	69 (67,6%)
Yes	163 (46,2%)	103 (55,4%)	27 (41,5%)	33 (32,4%)
Menarche*				
≤12 years	124 (35,1%)	84 (45,2%)	17 (26,2%)	23 (35,8%)
> 12 years	229 (64,9%)	102 (54,8%)	48 (73,8%)	79 (77,5%)
First sexual intercourse*				
≤15 years	130 (36,8%)	85 (45,7%)	21 (32,3%)	24 (23,5%)
> 15 years	223 (63,2%)	101 (54,3%)	44 (67,7%)	78 (76,5%)
Number of pregnancies*				
≤ 3	248 (70,3%)	162 (87,1%)	43 (66,2%)	43 (42,2%)
>3	105 (29,7%)	24 (12,9%)	22 (33,8%)	59 (57,8%)

Number of children*				
≤ 3	277 (78,5%)	171 (91,9%)	53 (81,5%)	53 (52%)
>3	76 (21,5%)	15 (8,1%)	12 (18,5%)	49 (48%)
Number of partners				
≤ 3	223 (63,2%)	111 (59,7%)	40 (61,5%)	72 (70,6%)
>3	130 (36,8%)	75 (40,3%)	25 (38,5%)	30 (29,4%)
Contraceptive use*				
No	141 (39,9%)	50 (26,9%)	27 (41,5%)	64 (62,7%)
Yes	212 (60,1%)	136 (73,1%)	38 (58,5%)	38 (37,3%)
Condom use*****				
No	252 (71,4%)	104 (55,9%)	58 (89,2%)	90 (88,2%)
Yes	101 (28,6%)	82 (44,1%)	7(10,8%)	12 (11,8%)
Previous STI*				
No	214 (60,6%)	56 (30,1%)	64 (98,5%)	94 (92,2%)
Yes	139 (39,4%)	130 (69,9%)	1 (1,5%)	8 (7,8%)
Had received a preventive gynecological exam				
No	71 (20,1%)	34 (18,3%)	13 (20%)	24 (23,5%)
Yes	282 (79,9%)	152 (81,7%)	52 (80%)	78 (76,5%)
HPV*				
Positive	210 (59.5%)	105 (56.4%)	39 (60%)	66 (64.7%)
Low risk	31 (14.8%)	13 (12.4%)	5 (12.8%)	13 (19.7%)
High risk	67 (31.9%)	41 (39%)	15 (38.5%)	11 (16.7%)
Undetermined	112 (53.3%)	51 (48.6%)	19 (48.7%)	42 (63.3%)
Negative	143 (40.5%)	81 (43.6%)	26 (40%)	36 (35.3%)

Data in proportion format were evaluated using the chi-square and Fisher's exact tests. * $P< 0.05$.

Table 2 presents sexual and reproductive characteristics associated with women´s reproductive stage groups. Tabagism was more common in the postmenopausal group but lesser for alcohol consumption ($P< 0.05$). They had their menarche usually after 12 years and their first intercourse after 15 years old ($P< 0.05$). Conversely, they had more pregnancies and children ($P< 0.05$). The use of contraceptives as well as condoms was less common in the postmenopausal group ($P< 0.05$). Fertile women reported more previous STIs than did climacteric and postmenopausal women ($P< 0.05$).

HPV DNA was present in more than half of the women (59.8%) and was higher in the postmenopausal group (65.7%; $P< 0.05$). However, when we separately evaluate the incidence of HPV according to the type, high-oncogenic HPV (HR HPV) was more common in women in the fertile and climacteric groups, 39% and 38.5%, respectively, compared to 16.7% of postmenopausal women (Table 2).

Genotyping revealed that the fertile group had a greater variety of genotypes than that in the non-fertile group (Figure 1). Among the HPV genotypes, 10 were exclusively present in the fertile age group, five in the menopause group, and only one was exclusively in the climacteric group. HPV 16 was the most prevalent in the general population and fertile and climacteric women. In the postmenopausal group, HPV 70, with low oncogenic risk, was the most prevalent, followed by HPV 16 (Figure 1).

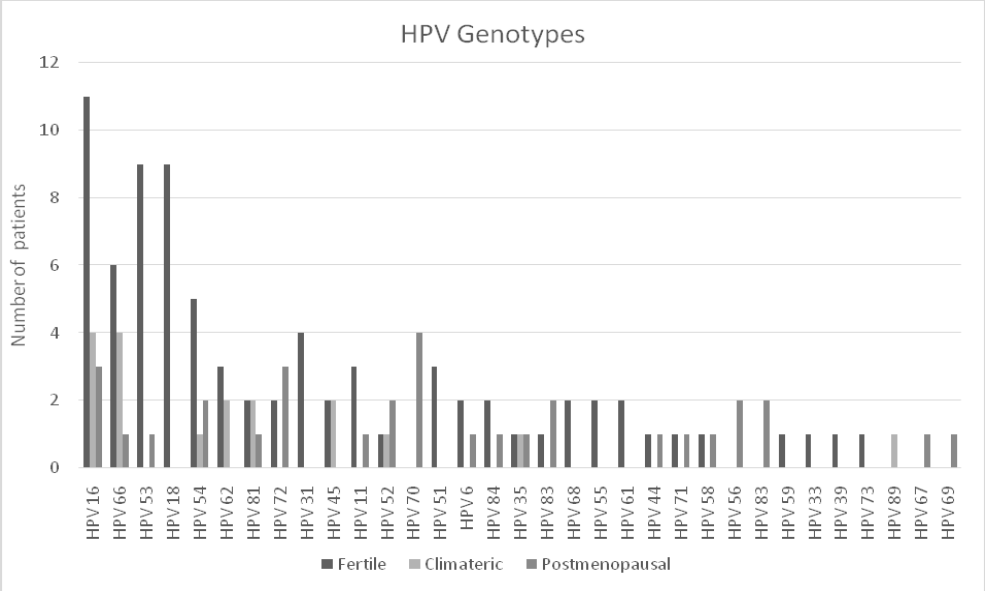

Figure: 1

Cytological analysis revealed that 6.8% of the samples showed cytological alterations, with no statistical difference between the groups (Table 3). *Gardnerella sp.* were significantly more abundant in the fertile age group ($P< 0.05$).

Table 3. Data from cytological analysis from participants stratified based on the stage of reproduction.

	Total N = 353	**Fertile Age N = 186**	**Climacteric N = 65**	**Postmenopause N = 102**
*Gardnerella sp.**				
No	246 (69.7%)	109 (58.6%)	45 (69.2%)	92 (90.2%)
Yes	107 (30.3%)	77 (41.4%)	20 (30.8%)	10 (9.8%)
Candida sp.				
No	277 (78.5%)	145 (78%)	50 (76.9%)	82 (80.4%)
Yes	76 (21.5%)	41 (22%)	15 (23.1%)	20 (19.6%)
Trichomonas vaginalis				
No	343 (97.2%)	179 (96.2%)	62 (95.4%)	102 (100%)
Yes	10 (2.8%)	7 (3.8%)	3 (4.6%)	0 (0%)
CellAtypia				
Normal	328 (93.2%)	171 (91.9%)	61 (93.8%)	96 (94.1%)
Abnormal	25 (6.8%)	15 (6.8%)	4 (6.2%)	6 (5.9%)
ASC-H	6 (1.7%)	4 (2.15%)	0 (0%)	2 (1.96%)
ASC-US	9 (2.6%)	6 (3.22%)	2 (3.08%)	2 (1.96%)
HSIL	2 (0.2%)	0 (0%)	1 (1.5%)	1 (0.98%)
LSIL	8 (2.3%)	5 (2.69%)	2 (3.08%)	1 (0.98%)

Data represented as proportion evaluated using the chi-square and Fisher's exact tests. *$P< 0.05$

The statistically significant variables were subjected to multivariate analysis to assess the probability of these variables belonging to the postmenopausal group compared to the fertile and climacteric groups (Tables 4 and 5, respectively).

Table 4. Multivariate analysis in females of the fertile group comparing females of the postmenopausal group

Fertile Age				
Variables	**Odds ratio**	**IC (95%)**	**Wald**	**P-value**
Monthly income				
No income	9,532	2,890-31,442	13,710	**0,000**
≤1 minimum wage	2,616	1,020-6,712	4,002	**0,045**
>1 minimum wage	*	*	*	*
Education level				
Illiterate	0,010	0,000-0,697	4,528	**0,033**
Elementary school complete/incomplete	0,132	0,021-0,819	4,729	**0,030**
Secondary school complete/incomplete	0,378	0,066-2,154	1,201	0,273
Graduate school complete/incomplete	*	*	*	*
Smoking status				
No	3,310	1,176-9,310	5,143	**0,023**
Yes	*	*	*	
Alcohol consumption				
No	0,449	0,191-1,056	3,370	0,066
Yes	*	*	*	*
Number of pregnancies				
≤ 3	5,212	1,928-14,091	10,584	**0,001**
>3	*	*	*	*
Contraceptive use				
No	0,599	0,255-1,407	1,385	0,239
Yes	*	*	*	*
Condom use				
No	0,314	0,115-0,857	5,113	**0,024**
Yes	*	*	*	*
Previous STI				
No	0,019	0,006-0,063	41,753	**0,000**
Yes	*	*	*	*
HPV				
Positive				
Low risk	0,125	0,019-0,808	4,772	**0,029**
High risk	7,389	1,114-49,018	4,291	**0,038**
Intermediary	0,489	0,106-2,254	0,842	0,359
Undetermined	0,691	0,272-1,752	0,608	0,436
Negative	*	*	*	*
Gardnerella sp.				
No	0,010	0,000-0,697	16,496	**0,000**
Yes	*	*	*	*

*Reference category in the analysis of variables

Women in the fertile group had no income (28%; 95 % CI 2.890–31.442; *P*< 0.000) or received less than the minimum Brazilian wage (34.9%; 95% CI 1.020–6.712; *P* = 0.045) compared to the postmenopausal group. Conversely, fertile women group had more years of education and were non-smokers (76.9%; 95% CI 1.176–9.310; *P*< 0.023). They also had a smaller number of pregnancies (95% CI 1.928–14.091; *P*< 0.001), tended to use condoms during sexual intercourse (95% CI 0.115–0.857; *P*< 0.024), and reported more previous occurrences of STIs (95% CI 0.006–0.063; *P*< 0.000).

Fertile women had a higher risk of HR HPV infection (39%; 95% CI 1.114–49.018; *P*< 0.038) but less for LR HPV (12.4%; 95% CI 0.019–0.808; *P*< 0.029). *Gardnerella* sp. infection was less common in postmenopausal women (58.6%; 95% CI 0.034–0.306; *P*< 0.000) (Table 4).

A similar statistical analysis was applied to compare the postmenopausal and climacteric groups (Table 5). Fewer statistical differences were observed between these groups.

Table 5. Multivariate analysis in females of the climacteric group comparing females of the postmenopausal group.

Climacteric Age				
Variables	**Odds ratio**	**IC (95%)**	**Wald**	**P-value**
Monthly income				
No income	1,447	0,463-4,521	0,403	0,525
≤1 minimum wage	2,208	0,960-5,076	3,478	0,062
>1 minimum wage	*	*	*	*
Education level				
Illiterate	*	*	*	*
Elementary school complete/incomplete	0,279	0,043-1,795	1,805	0,179
Secondary school complete/incomplete	0,390	0,063-2,407	1,029	0,062
Graduate school complete/incomplete	*	*	*	*
Smoking status				
No	5,336	2,033-14,003	11,568	**0,001**
Yes	*	*	*	*
Alcohol consumption				
No	0,619	0,282-1,356	1,438	0,231
Yes	*	*	*	*
Number of pregnancies				
≤ 3	1,868	0,833-4,187	2,303	0,129
>3	*	*	*	*
Contraceptive use				
No	0,437	0,204-0,938	4,511	**0,034**
Yes	*	*	*	*
Condom use				
No	3,062	0,970-9,662	3,641	0,056
Yes	*	*	*	*
Previous STI				
No	5,561	0,605-51,078	2,300	0,129
Yes	*	*	*	*
HPV				
Positive				
Low risk	0,414	0,096-1,780	1,405	0,236
High risk	8,123	1,329-49,660	5,142	**0,023**
Intermediary	0,765	0,205-2,850	0,160	0,689
Undetermined	0,535	0,227-1,264	2,033	0,154
Negative	*	*	*	*
Gardnerella sp.				
No	0,187	0,065-0,538	0,854	0,355
Yes	*	*	*	*

*Reference category in the analysis of variables

Differences were observed concerning cigarette and contraceptive use and HR HPV presence. Smoking was less common in the climacteric group (84.6%; 95% CI 2.033–14.003; $P< 0{,}005$); and they usually use contraceptives (58.5%; 95% CI 0.204–0.938; $P< 0.005$). They also had more HR HPV infection (38.5%; 95% CI 1.329–49.660; $P< 0.005$) than the postmenopausal group.

4. Discussion

Studies reveal that the incidence of HPV presents two peaks, around the age of 25 years, and a new peak after the age of 45 years (Bruni et al., 2010). In this study, sociodemographic characteristics and risk factors associated with HPV infection were compared among women at different stages of the reproductive cycle. Postmenopausal women had a lower educational index, higher smoking habit, greater number of pregnancies, and displayed less use of contraceptives, including condoms when compared to that in fertile and climacteric groups. All of these are known risk factors for HPV infection (de Sanjosé et al., 2018).

Furthermore, HPV prevalence, regardless of high or low risk, was significantly higher in the postmenopausal group. Physiological changes in the female reproductive tract, decreased immunity which occurs naturally with age, and risky behaviors may be responsible for a new HPV infection and/or reactivation in this age group (Awua et al., 2017; Hale & Burger, 2009; Sivro et al., 2013). When analyzing the incidence of HPV due to oncogenic risk, younger women from fertile and climacteric groups had more HR HPV infections while LR HPV was associated with postmenopausal status. A recent study carried out in China with 4614 pre-and post-menopausal women revealed that the virus diversity was similar in the two groups, with type 39 being more prevalent in postmenopause (Shen et al., 2021). Our results differed, as a greater variety of HPV was observed in the fertile age group. They also demonstrated no significant difference between the infection rates in pre- and postmenopausal women (Shen et al., 2021).

Corroborating our findings, large population-based studies demonstrated that the mean prevalence of oncogenic HPV types was high in the youngest women but decreased in middle-aged women. The second peak of infection in older women is more pronounced for non-oncogenic types(3,15,16). We suggest that the increase of HPV infection in the postmenopausal group is mainly due to LR types.

Some HPV-positive samples could not be identified using the automatic sequencing genotyping technique. This may be due to the presence of other infections in these samples, which prevent the detection of the virus, as described by Gharizadeh et al. (2005) and Verteramo et al. (2009). Multiple HPV genotypes commonly coexist within the cervical epithelia and are frequently detected together in smears (Schmitt et al., 2013). HPV infection rates are higher in developing regions than in the developed, which is true for women with both normal or abnormal cytology (Asiaf et al., 2014; de Sanjosé et al., 2007; Kombe Kombe et al., 2021; Rahmat et al., 2021). Indeed, despite the high prevalence of HPV, 93.2% of the population showed normal cytological findings.

A significantly higher presence of *Gardnerella* sp. was detected in the fertile group. Studies have demonstrated that the progression of precancerous lesions is associated with a subsequent increase in microbiota variability, specifically *Gardnerella vaginalis* bacteria and some pathogenic fungi (Kombe Kombe et al., 2021; Usyk et al., 2020). Our work suggests that fertile women may be at an increased risk of developing cervical malignant lesions as they have more *Gardnerella* and HR HPV infections. Studies involving genotypic analysis of HPV are important for estimating the effectiveness of current vaccines. The importance of the effective implementation of screening programs for both women and men for the early detection of (pre)neoplastic lesions caused by HPV is also emphasized.

5. Conclusion

Incidence of HPV was high, being more present in postmenopausal women. However, when assessing the type of HPV, a higher prevalence of high-risk types was observed in non-menopausal women. Several risk factors associated with HPV infection were present, such as low level of education, smoking habit, greater number of pregnancies, and no use of condoms. Despite the high incidence of HPV, cytological abnormalities were scarce.

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