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Abstract

Background

High-risk human papillomavirus (HR-HPV) are responsible for cervical cancer (CC), that is a major health problem worldwide and the second most prevalent gynecological cancer among Tunisian women. Preventive tools against CC are based on screening and prophylactic vaccines. Improving the preventive strategies as well as the therapeutic algorithms needs the understanding of HPV distribution in cervical lesions in Tunisian women.

Methods

A total of 200 formalin-fixed paraffine embedded biopsies were collected in our study. DNA was extracted using Qiagen Mini prep kit. DNA quality was controlled by Beta Globin PCR. Only positive samples for Beta Globin test were used. HPV detection was performed by a nested PCR using PYGMY and GP5+/6+ primers. Genotyping was performed by Reverse Line hybridization using 31 probes.

Results

The mean age of participants was 38.97 years and 54.5% were over 40 years. Cervical neoplasia distribution according to age showed that CINII/CINIII was observed in women over 30 years old. All samples were positive for Beta Globin PCR. Global HPV prevalence in cervical lesions was 83% (166/200). HPV was present in 65% in CINI, 82% in CINII/CINIII and 85% in CC. HR-HPV was statically associated with cervical intraepithelial neoplasia ($p<10^{-3}$). HR-HPV distribution according to lesion grade and cervical cancer showed that HPV16 and HPV18 were present in all lesions. For CINII/CINIII, HPV 35 (33,33%) was the most detected type, followed by HPV18 (28,6%), HPV 45 (25%) and HPV 16 (21,7%). HPV 45(62%), HPV 18 (47%) were the most detected in CC. HPV58, 59, 66 were only detected in CC and associated with HPV45,18 and HPV16. HPV39, 31, 33, 52, 56, 68 and HPV70 was associated only with CINI.

Conclusions

These findings show that HR-HPV represents 54,6 % of all infections in all cervical lesions. Five HR-HPV (35, 18, 45,16, 51) were detected in CINII/CINIII with a high incidence of HPV 35, 18, 45, and 16 that are included in the proposed vaccines. These findings give useful information for vaccine implementation consideration as well as personalized decision algorithms of intra-epithelial cervical lesions in Tunisian women.

Background

Cervical cancer (CC) is the second gynecological cancer in women worldwide [1, 2] with a global annual incidence of 569,847 in 2018, and 311,365 annual death rate [3]. In Northern Africa, the incidence of CC is

7652 cases with 5243 deaths annually [3]. Among Tunisian women, CC ranks fourth after breast, lung and colorectal cancer [4], with 299 new cases each year and about 200 deaths per year[5–7].

Pap smear screening has not been successful for preventing CC in Tunisian women. It seems necessary to offer new epidemiological considerations that could possibly include vaccine implementation and HPV testing in a global efficient preventive strategy.

It is well known that HPV is the first causal agent of CC [8]. About 201 different HPV types have been identified. More than 40 types infect the mucous membranes and have been classified into Low-risk (LR-HPV) and High-risk (HR-HPV) depending on their ability to induce malignant progression [9, 10]. Most HPV infections are cleared with the immune system response. Cervical intraepithelial neoplasia (CIN) is a progressive pathophysiological process with two different pathways [11] .The first one is a spontaneous regression of the cervical lesions. The second is the persistence of the infection with a HR-HPV that can progress to high grade intraepithelial neoplasia (CINII, CINIII) and CC in 8 to 12 years [10, 12, 13].

As HPV infection prevalence and genotype distribution is known to vary significantly in different countries and world regions [14, 15] their investigation in specific areas provides a scientific basis for the measures and methods an efficient preventive and therapeutic strategy including vaccine implementation and HPV testing. Prevalence and distribution of HPV types in different stages of cervical intraepithelial neoplasia has not yet been studied in Tunisia to our knowledge. This work aims to provide Tunisian scientific data that can be useful for an efficient management of cervical intra-epithelial lesions in Tunisian women.

Methods

Population study

This is a retrospective study including 200 women aged between 19 ~ 59 years old with cervical intraepithelial neoplasia diagnosed on biopsies. Samples are paraffin embedded blocks that were collected between 2016 and 2019 in the department of pathology of Pasteur Institute of Tunis. Cervical intraepithelial neoplasia was classified according to the Bethesda system [16] as bellow (Table 1):

Table 1
Samples number according to cervical intraepithelial neoplasia.

Cervical lesion	CINI	CINII/CINIII	CC	Total
Number	82	92	26	200

DNA Extraction

Paraffin blocks were cut into 10µm thin preparations. The rewashing step was performed by three washing baths in Xylen (incubation at 65°C for 15 min) followed by four washings with ethanol with

decreasing concentrations. DNA was then extracted by Qiagen Mini prep kit according to the manufacturer's instructions. The DNA quality was evaluated by a beta-globin test using specific primers PC04/GH20. DNA purity was measured by Nanodrop spectrophotometer.

HPV DNA detection and typing

HPV detection used a nested PCR with PGMY 09/11 primers for the first PCR and biotinylated GP5+/GP6 + for the second PCR. PCR was performed with a positive control (plasmid with HPV) and a negative control. The first PCR cycling parameters were composed of 1min initial denaturation at 94°C, followed by 30 amplification cycles of 30s at 94°C, 2 min at 54°C and 1 min at 72°C. This reaction was followed by a nested PCR using 10µl of the PGMY PCR product in a reaction mixture containing 50µmol of GP5+/GP6 + primers, 3 mM Mgcl2, 1.5mM each of the dNTP, 1U of Taq DNA polymerase and 5µl of Taq DNA polymerase buffer. The PCR cycling parameters contained a 4 min initial denaturation followed by 40 cycles of 30s at 94°C, 1 min at 50°C, 1min30s at 72°C and a final extension step for 10 min at 72°C. Molecular genotyping was performed on samples that had positive signal amplification with the nested PCR and used a Reverse blotting hybridization as described in the Human Papillomavirus Laboratory Manual published by the WHO (World Health Organization). 15µl denatured PCR products could hybridize with primers probes specific for 31 HPV types (HPV6, 11, 16, 18, 26, 31, 33, 34, 35, 39, 40, 42, 44, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 66, 68, 69, 70, 73, 82, 83 and 84), immobilized on a Biodyne C membrane using a Miniblotter MN45. The hybridized DNA was detected using streptavidin peroxidase and ECL.

Statistical study

Statistical analyses used the Statistical Package for the Social Sciences (SPSS) software version 20.0 (IBM, Somers, NY, USA). Pearson's chi-square test was calculated to associate HPV detection and HPV genotypes with different variables. P values < 0.05 were considered statistically significant.

Ethical considerations

The study was approved by the Ethical committee of Institut Pasteur de Tunis (2018/03/LAPHEIPT) and conducted with good clinical practice, ensuring confidentiality and anonymity.

Results

1. Population study

A total of 200 samples were collected for this study from women aged between 19 and 59 years old. The mean age of participants was 38.97 years and 54.5% were over 40 years.

Cervical neoplasia distribution according to age showed that CINII/CINIII were observed in women over 30 years old (Table 2). No statistical significance between age and lesions was found ($p > 0.05$).

Table 2
Intraepithelial cervical lesions distribution according to age group

		CINI	CINII/CINIII	Cervical cancer	Total
Age group	**<=30**	31.6%	57.9%	10.5%	100.0%
	]30–40]	17.1%	63.4%	19.5%	100.0%
	]40–50]	8.3%	61.1%	30.6%	100.0%
	> 50	0.0%	66.7%	33.3%	100.0%

CINI: Cervical intraepithelial neoplasia I, CINII: Cervical intraepithelial neoplasia grade II, CINIII: Cervical intraepithelial neoplasia grade III.

2. Global HPV prevalence

All samples were positive for the βglobin test. HPV detection and typing were performed for 200 samples. HPV was detected in 166 samples leading to a global prevalence of 83%.

The mean age of HPV positive women was 39.56 years old. The most prevalent age group within HPV positive women was < 30 and > 50 (Fig. 1) without statistical significance ($p > 0.05$).

HPV was present at the rate of 65% in CINI. For CINII/CIN III and CC HPV prevalence was respectively 82% and 85% (Fig. 2).

3. HPV genotype distribution

A total of 22 genotypes was identified and were classified into HR-HPV types and LR-HPV (Fig. 3).

Multiple and single infections were detected respectively in 43% and 57% of cases. No statistical association between infection type and age group or cervical intraepithelial neoplasia (Table 3) was found. HR-HPV and LR-HPV prevalence were respectively 54.6% and 65.4%.

Table 3
Infection type distribution according to age group.

	Infection type			p
Age group		**Multiple infection**	**Single Infection**	
	< 30	63.2%	36.8%	
	30–39	56.1%	43.9%	0.8
	40–50	52.8%	47.2%	
	> 50	50.0%	50.0%	
Cervical intraepithelial neoplasia	CINI	13.3%	20%	0.16
	CINII/CINIII	68.1%	61.7%	
	CC	25%	11.4%	

CINI: Cervical intraepithelial neoplasia I, CINII: Cervical intraepithelial neoplasia II, CINIII: Cervical intraepithelial neoplasia grade III, p: p value for the association between HPV type infection, age and cervical neoplasia.

The prevalence of HR-HPV and LR-HPV was respectively 54.6% and 65.4%. HR-HPV was associated with cervical intraepithelial neoplasia ($p < 10^{-3}$).

The most prevalent LR-HPV type was HPV 6 followed by HPV11, 42, 40, 43 and HPV 54 (Fig. 3). LR-HPV were prevalent in the age group (30–40) (Fig. 1).

The predominant HR-HPV were HPV 16, 18, 53, 35, 45, 39, 51, 52, 33, 59, 68, 70, 66 and HPV 56. HR-HPV were observed mostly in women in the age group (40–50) (Fig. 1).

4. HR HPV- types distribution according to cervical intraepithelial neoplasia

HR-HPV distribution according to CIN and CC showed that HPV 16 and HPV18 were present in all grades (Table 4.). They were associated with HPV58, HPV59, HPV66 which were present only in CC. HPV 39, 31, 33, 52, 56, 68 and HPV70 were detected only in CINI (Table 4). For CINII/CINIII, HPV 35 (33,33%) was the most detected type, followed by HPV18 (28,6%), HPV 45 (25%) and HPV16 (21,7%). HPV 45(62%), HPV 18 (47%) and HPV16 (26,1%) were the most detected in CC.

Table 4
Distribution of HR-HPV types according to cervical intraepithelial neoplasia

Cervical intraepithelial neoplasia			
HPV Type	**CC**	**CINI**	**CINII/CINIII**
HPV16	26.1%	52.2%	21.7%
HPV18	47.6%	23.8%	28.6%
HPV31	0.0%	100.0%	0.0%
HPV33	0.0%	100.0%	0.0%
HPV35	33.3%	33.3%	33.3%
HPV39	0.0%	100.0%	0.0%
HPV45	62.5%	12.5%	25.0%
HPV51	0.0%	85.7%	14.3%
HPV52	0.0%	100.0%	0.0%
HPV53	33.3%	66.7%	0.0%
HPV56	0.0%	100.0%	0.0%
HPV58	100.0%	0.0%	0.0%
HPV59	100.0%	0.0%	0.0%
HPV66	100.0%	0.0%	0.0%
HPV68	0.0%	100.0%	0.0%
HPV70	0.0%	100.0%	0.0%

CINI: Cervical intraepithelial neoplasia I, CINII: Cervical intraepithelial neoplasia II, CINIII: Cervical intraepithelial neoplasia III.

Discussion

Cervical cancer is a multistep disease and persistent infection with HR-HPV is the major cause of intraepithelial neoplasia and cervical cancer. An efficient preventive and therapeutic strategy including vaccine consideration and HPV testing needs to determine the HPV genotypes distribution in different cervical lesions. Previous Tunisian studies has been conducted on cervical cancer or women with normal pap smear [4, 17]. To our Knowledge, there is few epidemiologic data concerning HPV genotypes in cervical neoplasia from Tunisia. Our study provides results about HPV genotype distribution in different stages of cervical lesions that could be useful for a global preventive strategy of CC and therapeutic algorithms for CIN including vaccine implementation and HPV testing.

The mean age of participants in our study was 38.97 years and 54.5% were over 40 years. The mean age of HPV positive women was 39.56 years old. In our study population we found that there are two age peaks of HPV infection prevalence in women with cervical neoplasia: under 30 years old and over 50 years old. The infection rate during these ages was significantly higher than in the other age groups, suggesting a “U”-shaped infection. In most studies the highest peak is seen in younger women (under 25 years old) then a decreasing trend with age is observed and another maximum peak around 50 years old [18, 19].

In our population study, global HPV prevalence in cervical lesions was 83%. Our data showed that 65% of patients with CINI, 82% with CINII/CINIII and 85% with CC were HPV positive. These results are concordant with other studies conducted in center of Tunisia [1, 7–9, [20] which shows that global prevalence is 73,6%; 84% in CINI and 83,9% in CC. Our results are also consistent with those in most other studies in the word [21, 22]. A recent study in Morocco showed that HPV infection was 92,5% in CC [23]. The HPV positivity in Longnan-China women was 74,6% in CINI, 87,5% in CINII/CINIII and 89,05% in CC [24].

We can conclude that despite the small size of our subgroup, our results are consistent with most reports, which prove the performance of our method of HPV detection and genotyping. Our date reflects the real association pattern between HPV infection and cervical intraepithelial neoplasia subgroup.

Of all HPV positive simples, there was a great proportion of patients with multiple HPV types (43%), but without correlation between coinfection and age. This is not consistent with other studies [25], which showed age-specific prevalence of multiple HPV infections.

In our series HR-HPV was associated with cervical intraepithelial neoplasia ($p < 10^{-3}$). The predominant HR-HPV was HPV 16, 18, 53, 35, 45, 39, 51, 52, 33, 59, 68, 70, 66, 56. HR-HPV were observed in lower age < 30-year group and mostly in women in the age group (40–50). In a study of Guardado- Esatrada M, 2014 [26], it is reported that in CC Mexican patients, the first peak was found in the youngest women 35 ≤ years, the second peak was at 61–65 years and the mean ages of the patients singly infected with HPV16, HPV 18, HPV 45 and HPV 39 were at least 5 years lower than the patients singly or doubly infected with other HPV types and HPV 16, 18, 45 and 39 trends decrease [26]. In karollina Aro et al, 2019 study, it is reported that in CINII/CINIII HPV16 and HPV18 are more common in younger women under 30 years old then over 45 years old [25].

CINI may appear within 4 months after HPV infection and if associated with certain HPV genotypes, could progress to CINII, CINIII and cervical cancer. Assessing HPV genotype among CINI is therefore suitable to identify women at risk of progression. Our results indicate that the most frequent HPV genotypes in CINI in order of decreasing prevalence were HPV31, 33, 39, 52, 56, 68, 70, 51 and HPV 53. The meta-analysis [27] of Guan P et al, 2012 reported that HPV 35, 39, 51, 56 and 68 were present in low and High grade lesions but were low in CC, which prove the low carcinogenic potential of this types.

In our series the most prevalent genotypes in CINII/CINIII were HPV 35, 18, 45 and HPV16. In CC, HPV45, 18, 35 and HPV16 were predominant. HPV 16 and HPV18 were detected in all lesions. Our results are

concordant with the meta-analyses of Clifford GM.et al showing that in the fifteen high risk HPV genotypes, HPV16 and 18 were found in approximately 70% of cervical cancer worldwide [28]. We also demonstrate that HPV16, 18 and 45 were detected in CC. HPV45 is mostly present in CINII/CINIII and CC.

In fact, HPV 45 seems to be more frequent in Africa and less in European, American and Asian population [22, 24, 27]. In Europe, HPV16 and HPV18 are the most common types. HPV 58 is the most prevalent in Asia. In Saudi Arabia, the most common genotypes in CC were : HPV16, 18, 31, 45, 56, 59 and HPV73 [29]. In A worldwide meta-analysis of over 115 000 HPV-positive women HPV16, HPV18 were the most prevalent HPV types in cervical lesions, while HPV52 and HPV58 were most prevalent in East Asian women [14]. Other study in India describes HPV16, 18 and 58 as the most common types [15]. The Nano-valent vaccine seems to include all world regions HPV distribution [22, 24].

Our findings show that HPV16, 18, 45, 35, 51,53, 58, 59 and 66 HPV types detected in CINII/III and CC play an important role in the development of cervical cancer neoplasia in Tunisian women. Our results are concordant with other studies in the world [7, 11, 16, 17]. We also demonstrated the increased prevalence of HPV18 associated with CC which is less frequently represented in precancerous lesions as CINI and CINII/III. The higher risk for developing CINIII reported for HPV 18 was described in the Meta-analysis study of Clifford GM, 2003 [28].

Conclusions

Our results offer the basis to identify efficient clinical management approaches with HPV testing to avert cervical cancer in Tunisia also aiming to reduce the cost-effectiveness of current clinical care that supports cervical cancer prevention. Screening modalities and strategies, as well as clinical management algorithms, will need to evolve with a rational integration of HPV vaccination and cervical screening.

In this Tunisian series HR-HPV prevalence increases from CINI to CINII/CINIII and CC. HPV 35, 18, 45, 16 are the predominant HR-HPV in women with high grade intraepithelial cervical neoplasia CINII/CINIII. These results are meaningful for HPV test screening as well as personalized early decision algorithms and treatment of HR-HPV infected Tunisian women and can improve preventing progression into cervical cancer.

Abbreviations

HPV: Human papillomavirus

HR: High risk

LR: Low risk

CINI: Cervical Intraepthelial Neoplasea I

CIN II:Cervical Intraepthelial Neoplasea II

CINIII: Cervical Intraepthelial Neoplasea III

CC: Cervical Cancer

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90 DOI: 10.3322/caac.20107.
2. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348(6):518-27 DOI: 10.1056/NEJMoa021641.
3. GLOBOCAN CANCER OBSERVATORY. Cancer worldwide 2018 [Available from: https://gco.iarc.fr/databases.php.
4. Ennaifer E, Salhi F, Laassili T, Fehri E, Ben Alaya N, Guizani I, et al. Type-Specific Human Papillomavirus Distribution in Invasive Squamous Cervical Carcinomas in Tunisia and Vaccine Impact. Asian Pac J Cancer Prev. 2015;16(15):6769-72 DOI: 10.7314/apjcp.2015.16.15.6769.
5. GLOBOCAN.IARC. Cancer by population: Tunisia 2018 [Available from: https://gco.iarc.fr/today/data/factsheets/populations/788-tunisia-fact-sheets.pdf.
6. center Hi. Human Papillomavirus and related diseases Report: Tunisia 2019 [Available from: https://hpvcentre.net/statistics/reports/TUN.pdf.
7. Yazghich I, Berraho M. Cervical cancer in the Maghreb country (Morocco - Algeria - Tunisia) : epidemiological, clinical profile and control policy. Tunis Med. 2018;96(10-11):647-57.
8. zur Hausen H. Human genital cancer: synergism between two virus infections or synergism between a virus infection and initiating events? Lancet. 1982;2(8312):1370-2 DOI: 10.1016/s0140-6736(82)91273-9.
9. Raposo A, Tani C, Costa J, Mosca M. Human papillomavirus infection and cervical lesions in rheumatic diseases: a systematic review. Acta Reumatol Port. 2016;41(3):184-90.
10. Bosch FX, Burchell AN, Schiffman M, Giuliano AR, de Sanjose S, Bruni L, et al. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. Vaccine. 2008;26 Suppl 10:K1-16 DOI: 10.1016/j.vaccine.2008.05.064.
11. Campos NG, Burger EA, Sy S, Sharma M, Schiffman M, Rodriguez AC, et al. An updated natural history model of cervical cancer: derivation of model parameters. Am J Epidemiol. 2014;180(5):545-55 DOI: 10.1093/aje/kwu159.
12. Miller AB. The Natural History of Cervical Cancer. Cercival Cancer: From Etiology to Prevention. vol 2: Springer, Dordrecht; 2004. p. 61-78.
13. Castellsague X. Natural history and epidemiology of HPV infection and cervical cancer. Gynecol Oncol. 2008;110(3 Suppl 2):S4-7 DOI: 10.1016/j.ygyno.2008.07.045.

14. Grunberg MG, Chan M, Adhin MR. Distinctive distribution of HPV genotypes in cervical cancers in multi-ethnic Suriname: implications for prevention and vaccination. Epidemiol Infect. 2017;145(2):245-53 DOI: 10.1017/S0950268816002132.
15. Anderson LA, O'Rorke MA, Wilson R, Jamison J, Gavin AT, Northern Ireland HPVWG. HPV prevalence and type-distribution in cervical cancer and premalignant lesions of the cervix: A population-based study from Northern Ireland. J Med Virol. 2016;88(7):1262-70 DOI: 10.1002/jmv.24447.
16. Nayar R, Wilbur DC. The Bethesda System for Reporting Cervical Cytology: A Historical Perspective. Acta Cytol. 2017;61(4-5):359-72 DOI: 10.1159/000477556.
17. Ardhaoui M, Ennaifer E, Letaief H, Salsabil R, Lassili T, Chahed K, et al. Prevalence, Genotype Distribution and Risk Factors for Cervical Human Papillomavirus Infection in the Grand Tunis Region, Tunisia. PLoS One. 2016;11(6):e0157432 DOI: 10.1371/journal.pone.0157432.
18. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. Global burden of human papillomavirus and related diseases. Vaccine. 2012;30 Suppl 5:F12-23 DOI: 10.1016/j.vaccine.2012.07.055.
19. Chan PK, Chang AR, Yu MY, Li WH, Chan MY, Yeung AC, et al. Age distribution of human papillomavirus infection and cervical neoplasia reflects caveats of cervical screening policies. Int J Cancer. 2010;126(1):297-301 DOI: 10.1002/ijc.24731.
20. Missaoui N, Hmissa S, Trabelsi A, Tahar Yacoubi M, Nouira A, Frappart L, et al. [Prevalence of HPV infection in precancerous and cancerous lesions of the uterine cervix in Tunisia]. Ann Biol Clin (Paris). 2010;68(3):297-303 DOI: 10.1684/abc.2010.0431.
21. Guan P, Clifford GM, Franceschi S. Human papillomavirus types in glandular lesions of the cervix: a meta-analysis of published studies. Int J Cancer. 2013;132(1):248-50 DOI: 10.1002/ijc.27663.
22. Chen HC, You SL, Hsieh CY, Schiffman M, Lin CY, Pan MH, et al. Prevalence of genotype-specific human papillomavirus infection and cervical neoplasia in Taiwan: a community-based survey of 10,602 women. Int J Cancer. 2011;128(5):1192-203 DOI: 10.1002/ijc.25685.
23. Berraho M, Amarti-Riffi A, El-Mzibri M, Bezad R, Benjaafar N, Benideer A, et al. HPV and cofactors for invasive cervical cancer in Morocco: a multicentre case-control study. BMC Cancer. 2017;17(1):435 DOI: 10.1186/s12885-017-3425-z.
24. Zhao J, Guo Z, Wang Q, Si T, Pei S, Wang C, et al. Human papillomavirus genotypes associated with cervical precancerous lesions and cancer in the highest area of cervical cancer mortality, Longnan, China. Infect Agent Cancer. 2017;12:8 DOI: 10.1186/s13027-017-0116-y.
25. Aro K, Nieminen P, Louvanto K, Jakobsson M, Virtanen S, Lehtinen M, et al. Age-specific HPV type distribution in high-grade cervical disease in screened and unvaccinated women. Gynecol Oncol. 2019;154(2):354-9 DOI: 10.1016/j.ygyno.2019.05.024.
26. Guardado-Estrada M, Juárez-Torres E, Román-Bassaure E, Medina-Martinez I, Alfaro A, Benuto RE, et al. The distribution of high-risk human papillomaviruses is different in young and old patients with cervical cancer. PLoS One. 2014;9(10):e109406 DOI: 10.1371/journal.pone.0109406.

27. Guan P, Howell-Jones R, Li N, Bruni L, de Sanjose S, Franceschi S, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. Int J Cancer. 2012;131(10):2349-59 DOI: 10.1002/ijc.27485.
28. Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer. 2003;88(1):63-73 DOI: 10.1038/sj.bjc.6600688.
29. Alsbeih G, Al-Harbi N, El-Sebaie M, Al-Badawi I. HPV prevalence and genetic predisposition to cervical cancer in Saudi Arabia. Infect Agent Cancer. 2013;8(1):15 DOI: 10.1186/1750-9378-8-15.

Figures

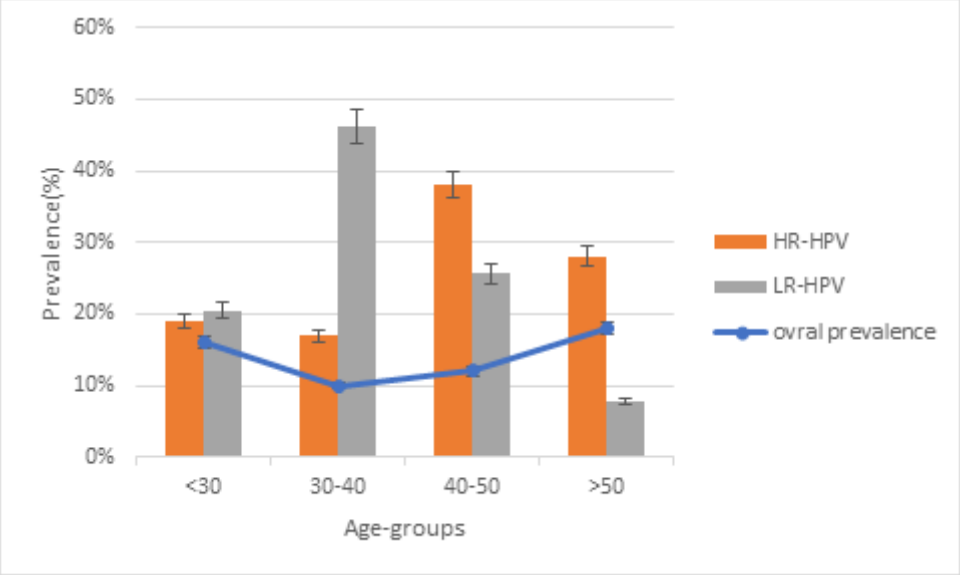

Figure 1

HPV prevalence distribution according to age groups

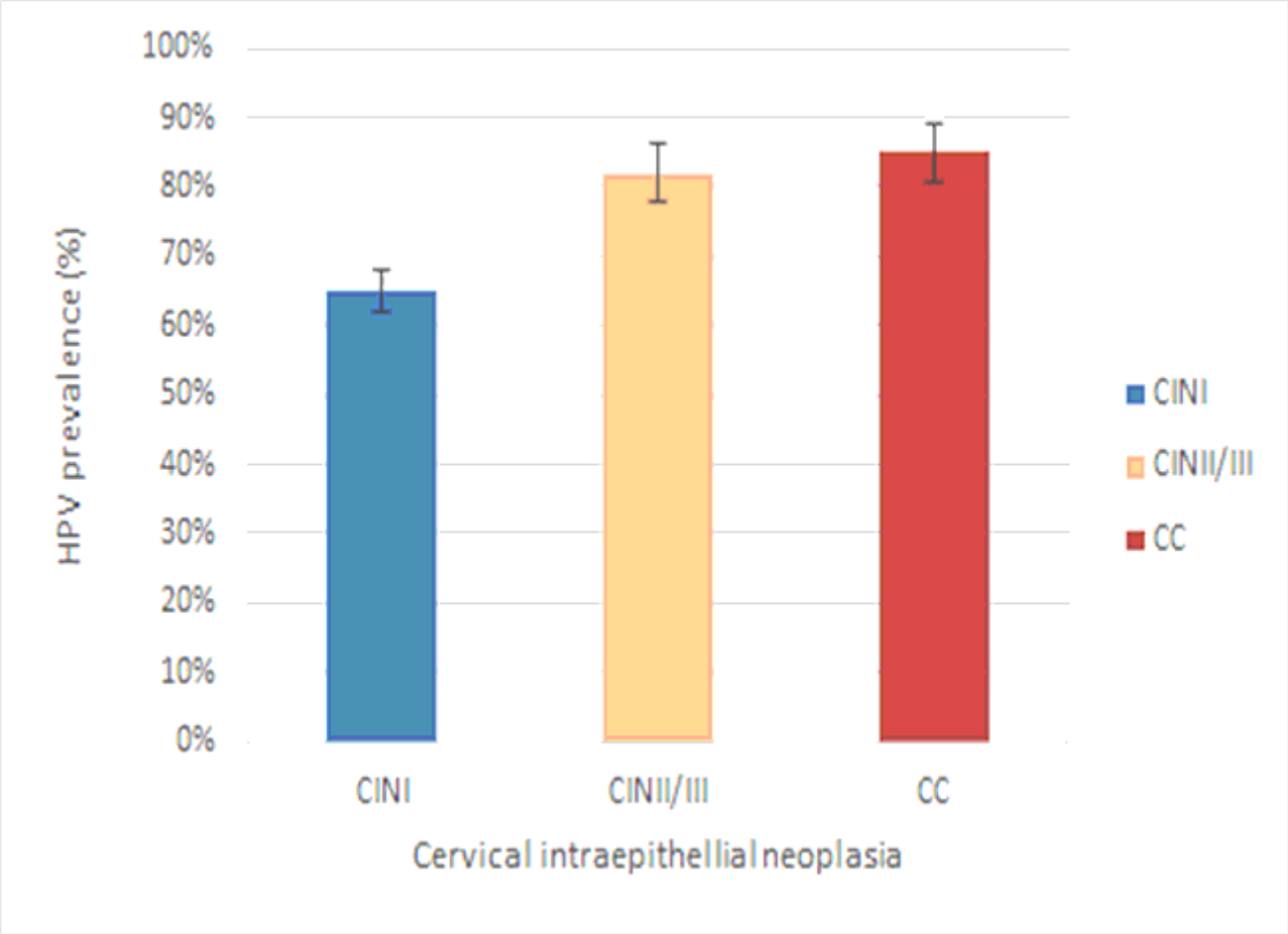

Figure 2

HPV prevalence according to the cytological statute

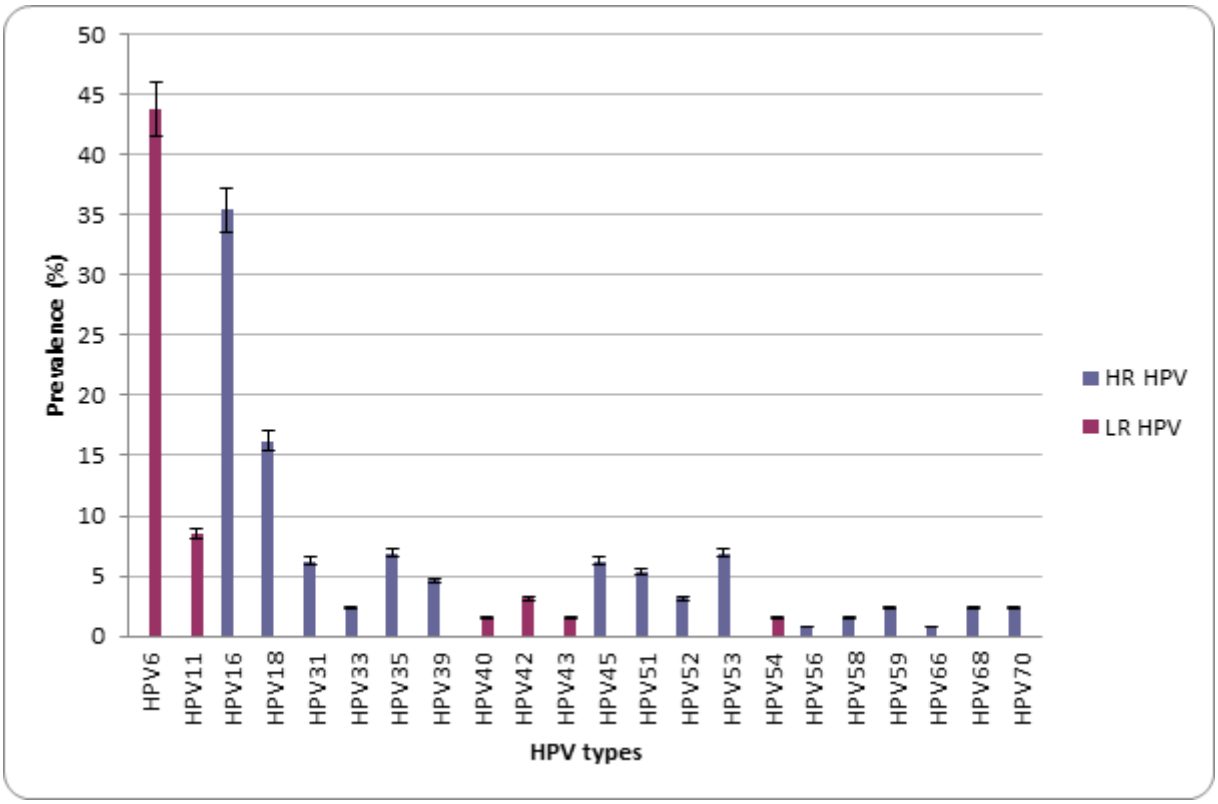

Figure 3

Distribution of HR-HPV and LR-HPV genotypes intraepithelial cervical neoplasia.