

# STATUS OF HUMAN PAPILOMA VIRUS IN A COHORT OF ROMANIAN WOMEN

GABRIELA ADRIANA DINCA<sup>1</sup>, DANIELA NUTI OPRESCU<sup>2</sup>,  
FLORENTINA LIGIA FURTUNESCU<sup>3</sup>, MATEI DUMITRU<sup>4</sup>

<sup>1,2,4</sup>National Institute for Mother and Child Health Alessandrescu – Rusescu, Bucharest,

<sup>2,3,4</sup>University of Medicine and Pharmacy "Carol Davila", Bucharest

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**Abstract:** Cervical cancer is the fourth most frequent type of cancer in women worldwide and its occurrence is strongly associated to high risk genotypes 16/18/31/33/35/39/45/51/52/56/58/59/66 of human papillomavirus (HPV). This observational study aimed to investigate the status of HPV infection in a cohort of 725 Romanian women requesting specialty services in a clinic of gynaecology from Bucharest. In our cohort, the HPV genotype 16 was by far most frequently identified and it was followed by genotypes 51, 31, 52 and 18 (prevalence of 37.5; 13.9; 13.4; 11.8; 10.6% respectively). Its presence increased significantly in women having HSIL cytology, compared to cases with less severe cytology results. We found also very low use of vaccination and HPV testing. Due to methodologic limitations, our results cannot be generalised in the Romanian women population and further research is needed for this purpose. However, our results suggest the need for a stronger public health approach for prevention and control of cervical cancer in Romania.

## INTRODUCTION

Cervical cancer is the fourth most frequent type of cancer in women worldwide, with an estimated of 528000 new cases and 260000 deaths reported for the year 2012.(1) This cancer is a source of major health inequities because 85% of the total cases occur in less developed regions of the world, meanwhile the three preceding most common tumours (breast, colorectal and lung) do occur with quite similar frequency in developed and less developed regions.(1,2)

By another hand, the deaths by cervical cancer are considered both amenable and preventable (potentially avoidable through good quality of health care services and adequate public health interventions respectively).(3)

Historically, main causes of cervical cancer were related to the age of starting the sexual life or to the number of partners, but, in the last two decades, strong evidence showed that human papillomavirus (HPV) is a necessary cause for this severe disease. The virus has over 200 genotypes which are classified as low and high risk respectively.(4) The virus has over 30 genotypes sexually transmitted and thirteen high risk genotypes, which were found to be responsible of 99.7% of the total cases of cervical cancer (HPV 16/18/31/33/35/39/45/51/52/56/58/59/66).(4-6) Among these genotypes HPV-16 and HPV-18 are the most common, being responsible of around 70% of all cervical cancers worldwide.(7)

Strategies for primary and secondary preventions are available for controlling the burden of cervical cancer, as programs for vaccination against HPV and populational screenings, either for cervical cancer (cytology based) or for HPV, last one bringing 70% more protection against invasive cervical cancer compared to cytology.(8)

Cervical cancer is a major public health problem in Romania, each year being reported over 3,500 new cases and 2400 deaths.(9,10) Even though at EU level deaths by cervical

cancer are considered amenable, the standardised mortality rate in Romanian women is more than three times higher compared to EU average (11.9 versus 3.1 deaths per 100,000 inhabitants respectively).(9,11) As regard the preventive strategies, they have limited availability. An attempt to initiate a program for vaccination against HPV targeting the girls of 9 – 11 years old was rejected by the civil society in 2008-2009, due to insufficiently analysed reasons. Apparently, the parents of the girls perceived the vaccine as risky or experimental and only 2.5% of the direct beneficiaries were vaccinated at that time.(12) The screening for cervical cancer using cytology is subject of a national health program since many years, but despite the gradual increase in number of beneficiaries, the at-risk population coverage remains still low, and with high disparities among regions (national coverage for period 2012 – 2015: 14.5% of eligible population, varying among regions from 7.4% to 22.6%).(13) Screening for HPV is not reimbursed by the health insurance, being available with full payment from the patient.

In this context, the prevalence of HPV infection and the distribution of different genotypes are not known in Romania, even though these data would be very necessary for monitoring the epidemiologic context and the impact of prophylactic vaccination.

## PURPOSE

Our study aimed to investigate the status of HPV infection in a cohort of Romanian women requesting specialty services in a clinic of gynaecology from Bucharest.

## MATERIALS AND METHODS

The presented study is a prospective cohort. All consecutive women seeking specialty gynaecologic services for cervical abnormalities during five years, since 1<sup>st</sup> of January

<sup>1</sup>Corresponding author: Gabriela Adriana Dinca, B-dul Lacul Tei, Nr. 120, Sector 2, București, România, E-mail: toyamed.gaby@yahoo.com, Phone: +4074 4347188

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2010 – 31<sup>st</sup> of December 2014 were enrolled.

The inclusion criteria were:

- Age over 18 years;
- Woman seeking specialty gynaecologic services for cervical abnormalities
- New case for the clinic at first visit.

We excluded pregnant women seeking pre-natal services.

The study is observational and it has been approved by the Ethical Committee of the Clinic.

We planned to have a two years' follow-up period. Within this interval each woman was invited to new visits depending on her clinical status and in accordance to the corresponding clinical protocols.

All the women have been investigated at enrolment following the medical protocol of the clinic, by receiving cytology, colposcopy and, if needed, recommendation for HPV testing. HPV testing was recommended at first visit to patients with abnormal cytology, or to patients with normal cytology and cervical lesion identified by colposcopy.

We collected data regarding personal characteristics (age at first visit, weight, height, education, living environment, smoking), personal antecedents (age of starting the sexual life, number of previous births or abortions, use of oral contraceptives, number of sexual partners, previously performed cytology, previously documented HPV infection and vaccination against HPV), clinical status at the enrolment visit (cytology, colposcopy, HPV testing) and therapeutic approach.

Cytology results were interpreted following the Bethesda reporting system as: NILM (Negative for Intraepithelial Lesion or Malignancy), ASCUS (Atypical squamous epithelial cells of uncertain significance)/ASC-H (Atypical Squamous Cells, Cannot Rule Out High-Grade Squamous Intra-epithelial Lesion), LSIL (Low-grade squamous intraepithelial lesion) and HSIL (high-grade squamous intraepithelial lesion). Colposcopy results were classified as: normal (without lesions), atypical transformation grade 1 (ATG1) and grade 2 (ATG2) areas.

For HPV testing we followed the presence of any of the thirteen known high risk genotypes 16/18/31/33/35/39/45/51/52/56/58/59/66, as single infection or coinfection.

The therapeutic approach included different pathways in accordance to clinical status of the patient, from the recommendation for a follow-up visit to histopathologic examination, associated or not to immunohistochemistry or surgical treatment. This paper presents only the clinical status and the status of HPV infection at the enrolment visit.

Data analysis: The scale variables were discussed as mean±SD or median and interquartile range. They were assessed for normality using the Kolmogorov-Smirnov test. A p-value <0.05 was considered for statistical significance (two tailed test). Categorical data were presented as proportions with one decimal. Proportions were compared by using Chi square test (p<0.05). Statistical analyses were performed using SPSS 23.0 and Open Epi.

**RESULTS**

We included in our cohort 725 women, seeking gynaecologic services during 2010 – 2014. The personal characteristics of the patients are shown in table no. 1.

Analysis of personal characteristics of the cohort reveals important differences compared to the general population, suggesting more favourable socio-economic determinants for the cohort. Most of our patients came from urban environment (91.3% vs. 55.1% in general population) and had tertiary education (70.3% vs. 26.8%).(14,15) Also the

proportion of smokers was almost double (27.9% compared to 16.7% in general female population respectively).(16)

**Table no. 1. Personal characteristics of the patients**

| Personal Characteristic              | Value                 |
|--------------------------------------|-----------------------|
| Age (years): mean±SD (min; max)      | 33.9±8.17 (18, 71)    |
| Weight (kg): mean±SD (min; max)      | 61.3±9.34 (43; 106)   |
| Height (cm): mean±SD (min; max)      | 165.7±5.36 (150; 185) |
| Body mass index: % (n)               |                       |
| underweight                          | 8.4% (n=61)           |
| normal weight                        | 73.4% (n=532)         |
| overweight                           | 14.3% (n=104)         |
| obese                                | 3.9% (n=28)           |
| Education*: % (n)                    |                       |
| Lower secondary or less:             | 1.7% (n=12)           |
| Upper secondary                      | 25.7% (n=186)         |
| Tertiary                             | 70.3% (n=510)         |
| Urban living environment: % (n)      | 91.3% (n=662)         |
| Prevalence of current smokers: % (n) | 27.9% (n=202)         |

\* Data available for 708 women

Personal antecedents of the patients are presented in table no. 2.

**Table no. 2. Personal antecedents of the patients**

| Personal Antecedents   | Value         |
|--|---------------|
| Age of starting the sexual life (years): median/IQR (min; max) | 19/2 (14; 38) |
| Previous births:   |               |
| Yes: % (n)   | 50.8% (n=368) |
| Births/person: median/IQR (min; max)                           | 1/1 (0; 6)    |
| Previous abortions:  |               |
| Yes: % (n)   | 43.6% (n=315) |
| Abortions/person: median/IQR (min; max)                        | 0/1 (0; 15)   |
| Use of oral contraceptives*:                                   |               |
| All ages: Yes % (n)  | 15.8% (n=111) |
| 18 – 29 years: Yes % (n)                                       | 25.7% (n=63)  |
| 30 – 39 years: Yes % (n)                                       | 13.9% (n=41)  |
| 40 – 49 years: Yes % (n)                                       | 5.1% (n=7)    |
| 50+ years: Yes % (n)   | 0% (n=0)      |
| Number of sexual partners:                                     |               |
| Partners/person: median /IQR (min; max)                        | 3/2 (0; 20)   |
| Previous cytology  |               |
| Yes: % (n)   | 13.7% (n=99)  |
| Previously documented HPV infection                            |               |
| Previous documented testing: % (n)                             | 12.4% (n=90)  |
| Positive results for HPV infection: % (n)                      | 11.4% (n=82)  |
| Positive results for high risk HPV genotype: % (n)             | 9.5% (n=69)   |
| **Single infection: % (n)                                      | 59.8% (n=49)  |
| **Coinfection: % (n)   | 40.4% (n=33)  |
| **Genotype 16: % (n)   | 41.5% (n=82)  |
| **Genotype 18: % (n)   | 17.1% (n=14)  |
| **Genotype 31: % (n)   | 14.6% (n=12)  |
| **Genotype 33: % (n)   | 6.1% (n=5)    |
| **Genotype 35: % (n)   | 1.2% (n=1)    |
| **Genotype 39: % (n)   | 1.2% (n=1)    |
| **Genotype 45: % (n)   | 4.9% (n=4)    |
| **Genotype 51: % (n)   | 4.9% (n=4)    |
| **Genotype 52: % (n)   | 4.9% (n=4)    |
| **Genotype 56: % (n)   | 0% (n=0)      |
| **Genotype 58: % (n)   | 6.1% (n=5)    |
| **Genotype 59: % (n)   | 1.2% (n=1)    |
| **Genotype 66: % (n)   | 12.2% (n=10)  |
| Previous vaccination   |               |
| Total cohort: % (n)  | 6.3% (n=46)   |
| Patients with documented infection: % (n)                      | 23.2% (n=19)  |
| Patients without documented infection: % (n)                   | 4.3% (n=27)   |

\* Data available for 705 women

\*\* Proportion was calculated among the positive results

## PUBLIC HEALTH AND MANAGEMENT

Among the personal antecedents, we noticed that half of the patients started their sexual life till the age of 19. Also half of them had already at least a birth, but 43.6% had at least an abortion in their past. Overall, 691 abortions and 522 births were registered among the study subjects, meaning a ratio abortion/birth of 1.3. These results suggest that abortion still remained popular as birth control method. These data are in line with the reduced proportion of oral contraceptive users. The use of gynaecology services was also limited, only 13.7% and 12.4% of the patients having a previous cytology and HPV documented testing respectively. As regard the HPV epidemiology, among the 82 cases with previous positive results, 59.8% had a single genotype and the rest had associations. Among the high-risk genotypes, 16, 18 and 31 were isolated most frequently. 6.3% of the patients were already vaccinated against HPV at the first visit.

### Clinical status at enrolment visit

At enrolment visit, the patients received cytology, colposcopy and, if needed, recommendation for HPV testing. Overall 721 and 715 patients received cytology and colposcopy respectively. The results are shown in table no. 3.

**Table no. 3. Results for cytology and colposcopy**

| Cytology        | Colposcopy |       |       |       |        |
|-----------------|------------|-------|-------|-------|--------|
|                 | Normal     | ATG1  | ATG2  | Total |        |
| Normal          | no         | 69    | 107   | 35    | 211    |
|                 | %          | 32.7% | 50.7% | 16.6% | 100.0% |
| ASCUS/<br>ASC-H | no         | 28    | 213   | 34    | 275    |
|                 | %          | 10.2% | 77.5% | 12.4% | 100.0% |
| LSIL            | no         | 4     | 95    | 41    | 140    |
|                 | %          | 2.9%  | 67.9% | 29.3% | 100.0% |
| HSIL            | no         | 0     | 14    | 75    | 89     |
|                 | %          | 0.0%  | 15.7% | 84.3% | 100.0% |
| Total           | no         | 101   | 429   | 185   | 715    |
|                 | %          | 14.2% | 60.0% | 25.9% | 100.0% |

As can be noticed, colposcopy confirmed in high proportion the severity of the HSIL lesions. 89.7% of the investigated patients (n=637) receive the recommendation for HPV testing, but only 78.2% of them (n=498) did perform the test. The results of the HPV testing are presented in table no. 4.

**Table no. 4. Results of the HPV testing**

| HPV testing characteristic               | Value                |
|--|----------------------|
| <b>*HPV testing:</b>                     |                      |
| Negative: % (n)                          | <b>14.9% (n=74)</b>  |
| Positive: % (n)                          | <b>85.1% (n=424)</b> |
| <b>**Type of infection:</b>              |                      |
| Positive – single infection: % (n)       | <b>49.8% (n=211)</b> |
| Positive – coinfection: % (n)            | <b>50.2% (n=213)</b> |
| Positive – high risk HPV genotype: % (n) | <b>89.9% (n=381)</b> |
| <b>**High risk HPV genotypes</b>         |                      |
| Genotype 16: % (n)                       | <b>37.5% (n=159)</b> |
| Genotype 18: % (n)                       | <b>10.6% (n=45)</b>  |
| Genotype 31: % (n)                       | <b>13.4% (n=57)</b>  |
| Genotype 33: % (n)                       | <b>6.1% (n=26)</b>   |
| Genotype 35: % (n)                       | <b>5.2% (n=22)</b>   |
| Genotype 39: % (n)                       | <b>2.8% (n=12)</b>   |
| Genotype 45: % (n)                       | <b>2.6% (n=11)</b>   |
| Genotype 51: % (n)                       | <b>13.9% (n=51)</b>  |
| Genotype 52: % (n)                       | <b>11.8% (n=50)</b>  |
| Genotype 56: % (n)                       | <b>4.0% (n=17)</b>   |
| Genotype 58: % (n)                       | <b>4.0% (n=17)</b>   |
| Genotype 59: % (n)                       | <b>3.3% (n=14)</b>   |
| Genotype 66: % (n)                       | <b>5.0% (n=21)</b>   |
| <b>**Most frequent result</b>            |                      |
| Genotype 16 – single infection: % (n)    | <b>18.9% (n=80)</b>  |

\* proportions calculated to N=498 (total tests)

\*\* proportions calculated to N=424 (positive tests)

More frequent genotypes were 16/51/31/52/18.

In our study recommendation for HPV testing has been addressed to patients with abnormal cytology or cervical lesion identified by colposcopy. However, only two thirds of patients with abnormal cytology have been tested (table no. 5).

Most frequent HR genotypes in abnormal cytology cases are shown in table no. 6.

**Table no. 5. HPV testing associated to cytology results**

| Cytology     | Total      | Tested     |              |
|--------------|------------|------------|--------------|
|              | no         | no         | %            |
| Normal       | 214        | 100        | 46.7%        |
| Abnormal     | 507        | 322        | 63.5%        |
| ASCUS/ASC-H  | 278        | 181        | 65.1%        |
| LSIL         | 140        | 83         | 59.3%        |
| HSIL         | 89         | 58         | 65.2%        |
| Missing      | 4          | 2          | NA           |
| <b>Total</b> | <b>725</b> | <b>424</b> | <b>58.5%</b> |

**Table no. 6. Most frequent high risk HPV genotypes in abnormal cytology**

| HPV genotype |    | ASCUS / ASC-H | LSIL  | HSIL  | p*   | p**   | p***    |
|--------------|----|---------------|-------|-------|------|-------|---------|
| 16           | no | 55            | 29    | 34    | 0.46 | 0.005 | < 0.001 |
|              | %  | 30.4%         | 34.9% | 58.6% |      |       |         |
| 51           | no | 29            | 14    | 6     | 0.86 | 0.28  | 0.29    |
|              | %  | 16.0%         | 16.9% | 10.3% |      |       |         |
| 31           | no | 27            | 9     | 7     | 0.37 | 0.57  | 0.82    |
|              | %  | 14.9%         | 10.8% | 12.1% |      |       |         |
| 52           | no | 26            | 14    | 2     | 0.6  | 0.01  | 0.02    |
|              | %  | 14.4%         | 16.9% | 3.4%  |      |       |         |
| 18           | no | 18            | 11    | 7     | 0.43 | 0.83  | 0.1     |
|              | %  | 9.9%          | 13.3% | 12.1% |      |       |         |

\*  $\chi^2$  for ASCUS/LSIL

\*\*  $\chi^2$  for LSIL/HSIL

\*\*\*  $\chi^2$  for ASCUS/HSIL

## DISCUSSIONS

This study is a non-interventional cohort, aiming to provide real-world data from the medical practice. The main goal was to analyse the status of HPV infection in 725 women seeking specialty gynaecologic services for cervical abnormalities.

Our subjects had a more privileged social statute compared to the general population of Romanian women, but despite this, we found high proportion of abortions and low use of oral contraception. Also very few women had a previous cytology or a documented HPV testing previous to the enrolment in the study and only 6.3% had been vaccinated against HPV. At enrolment, two thirds of the subjects had abnormal cytology and 84.3% of those having HSIL at cytology had been confirmed as ATG 2 by colposcopy. Despite the favourable social position, more than one fifth of the women with medical recommendation for HPV testing were not able to perform it, due to limited affordability.

The study has important limitations because we analysed a particular cohort, seeking specialty services for a previously known cervical lesion or abnormality. In addition, almost a quarter of the eligible women did not perform the HPV testing, so our conclusions refer only to the investigated women, but not to the overall cohort. From these reasons our conclusions cannot be generalized. However, the high-risk HPV genotypes 16/51/31/52/18 were most common in our subjects and this result seems to be consistent to other studies in European population, except for genotype 51, which was secondly most frequent in our subjects (table no. 7).

**Table no. 7. HPV genotypes prevalence in different studies**

| Study                         |      | 16   | 51   | 31   | 52   | 18   |
|-------------------------------|------|------|------|------|------|------|
| Our study                     | %    | 37.5 | 13.9 | 13.4 | 11.8 | 10.6 |
|                               | rank | 1    | 2    | 3    | 4    | 5    |
| Anderson et al. 2016 (17)     | %    | 37.4 | 3.9  | 8.2  | 6.8  | 5.1  |
|                               | rank | 1    | 5    | 2    | 3    | 4    |
| Castellague et al (2012) (18) | %    | 2.9  | 1.6  | 1.3  | 1.8  | NA   |
|                               | rank | 1    | 3    | 4    | 2    | NA   |
| Kjaer et al (2014) (19)       | %    | 5.4  | 3.4  | 3.8  | 3.9  | 2.4  |
|                               | rank | 1    | 4    | 3    | 2    | 5    |

The genotype 16 was by far most frequently identified either single or in coinfections. Its presence increased significantly in women having HSIL cytology. Per contrary, the presence of genotype 52 has decreased significantly in HSIL cases, but this result should be interpreted with caution due to the study limitations.

Despite the limitations, our results suggest that more importance should be awarded to cervical cancer as a public health problem, due to many reasons: very high mortality, very low coverage of the screening program, very low use of vaccination against HPV and limited access to testing (paid 100% by the patient).

### CONCLUSIONS

Cervical cancer is a public health problem worldwide and in Romania. Our analysis of a cohort of 725 women seeking specialty gynaecologic services for cervical abnormalities revealed that HPV high risk genotypes 16, 51, 31, 52 and 18 were most common. Genotype 16 was by far the most frequent and its presence increased significantly in women having HSIL cytology. In addition, we found very low use of vaccination and HPV testing. Due to methodologic limitations, our results cannot be generalised in the Romanian women population and further research is needed for this purpose. However, considering that in Romania the screening for cervical cancer has a very low coverage and the vaccination is available only with full direct payment from the beneficiary, the existing epidemiologic context requires planning a public health approach more focused on systematic prevention and control of cervical cancer.

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