

Epidemiological Aspects of Genital Warts in Romania – a 2012 Retrospective Survey

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ABSTRACT

Objectives: Genital infection with human papillomavirus (HPV) has become one of the most frequently viral sexually transmitted diseases. The infection may remain asymptomatic, may take the form of external genital warts and may give rise to cervical cancers. The aim of this study was to assess the frequency of the patients with genital warts addressing to five tertiary referral dermato-venereological units in Romania (where patients from several counties are referred) and to compare the results with the out-patient data reported by all Romanian hospitals.

Material and methods: Data regarding patients with external genital warts who addressed to the hospital emergency rooms, in five tertiary referral dermato-venereological units in Romania (Bucharest, Timisoara, Craiova, Constanta, Târgu-Mures) were collected for the year 2012. For comparison there have been used data collected by the National School of Public Health, Management and Professional Development, during the same year.

Outcomes: Data reported at national level in 2012 included 952 patients (731 women and 221 men) with 26 males under 20 years of age and 251 female patients in the age group 0-20 years. In the overall population (males and females combined) the total number of genital warts cases registered at the hospital emergency rooms in the five centers, in the year 2012, was 266 patients (119 men and 147 women) with 4 girls under 14 years of age and 6 male patients in the age group 0-14 years.

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Conclusions: *The high prevalence of the infection with HPV, the costs of treatment and the psychological impact prove that prevention of the disease is the most important step for decreasing the incidence of this disease. General measures for patients awareness regarding the disease and its complications need to be completed with the recommendation for vaccination. A closer monitoring of patients would provide information for a strategic national approach leading to a better outcome.*

Keywords: HPV, external genital warts, HPV vaccination, Romania

INTRODUCTION

External genital warts (EGW), also termed condyloma acuminata, represent ano-genital infections with human papillomavirus (HPV) and are the most common viral sexually transmitted disease found in the general population (1). HPV is a small, non-enveloped, double-stranded DNA virus; there are currently at least 100 distinct types that have been identified (2) and 30-40 of these are capable of infecting the ano-genital tract (3). The types of HPV can be grouped into three categories, according to their oncogenic potential: low risk (HPV 6, 11), intermediate risk (HPV 29, 31, 33, 45, 51, 56, 58, 59), high risk (HPV 16, 18): strongly associated with cervical, vulvar, vaginal and anal dysplasia. The risk of acquiring the infection is higher in individuals with many sexual partners, with other sexual transmitted diseases and in smokers (4). The treatment destroys mainly the visible lesions, without clearing the virus. The use of condoms does not totally eliminate the risk of infection. Due to the oncogenic potential of some HPV strains there is an increased interest in fighting this infection. Prophylactic vaccines against the most frequent HPV types involved in condyloma acuminata (HPV 6, 11) and in cervical cancer (HPV 16, 18) are now available and should be included in the vaccination schedule of all countries. In order to implement national measures of prophylaxis it is important to assess the extent of the infection in general population. In Romania the data from the general practitioner's offices are collected by the National Center for Statistics and Informatics in Public Health. The retrieval of information regarding EGW is not possible as this disease is reported using the ICD-9 under the code "53. Other muco-cutaneous viral infection" together with infectious skin diseases like: warts, herpes simplex, molluscum contagiosum, orf or milker's nodules. For the year 2012 there were 7634 patients (3429 (45%) males and 4205 (55%) females) (Table 1).

Other information can be obtained from the National School of Public Health, Management and Professional Development (NS-PHMPD) where data from all the hospitals in Romania are reported. These reports are performed under the ICD-10 and the code "A63.0. Ano-genital warts" clearly designates patients with EGW. However, data are referring only to patients admitted in hospitals giving no information on out-patients. In 2012 there were 952 patients admitted in hospitals with the diagnosis of EGW. Among them 731 (77%) were female and 221 (23%) were men; 261 patients had EGW as primary diagnosis and for 691 patients EGW was a secondary diagnosis (Table 2).

Few statistical analyses on HPV infection were performed in Romania. A PubMed search of key words "HPV, Romania, epidemiology" gave only 13 results, mainly with regional or local results and 9 of them being studies on cervical cancer. Because of the lack of a systematic review of the epidemiology of EGWs in the literature, we designed this study to shed light on this aspect. □

MATERIAL AND METHOD

Aretrospective statistical research on EGW was performed in the tertiary referral dermato-venerological hospital units of Bucharest (Colentina Clinical Hospital), Constanta, Timisoara, Targu Mures and Craiova. The data source is the Dermatology emergency room registry. The study covers the period January 01, 2012 – December 31, 2012. Those data are not available for the public and contain details regarding the patients' name, sex, age, health insurer, address and diagnosis. Epidemiological data were retrieved from those registries: sex, age groups and residence (urban or rural). The data were used to calculate the crude frequency of EGW for each hospital unit with stratification for sex, age groups and residence. In order to make possible the comparison with data from the NSPHMPD the age

	County	TOTAL	FEMALE	MALE	Age 0-11 mo	Age 1-14 yr	Age 15-64 yr	Age +65 yr
1	ALBA	149	73	76	6	46	91	6
2	ARAD	312	165	147	4	74	209	25
3	ARGES	247	123	124	3	99	124	21
4	BACAU	249	139	110	3	90	133	23
5	BIHOR	442	240	202	25	191	212	14
6	BISTRITA-NASAUD	60	33	27	0	22	35	3
7	BOTOSANI	226	131	95	3	80	127	16
8	BRASOV	320	157	163	55	127	118	20
9	BRAILA	91	56	35	2	35	41	13
10	BUZAU	85	45	40	23	20	39	3
11	CARAS-SEVERIN	53	25	28	0	28	22	3
12	CALARASI	54	28	26	1	11	41	1
15	COVASNA	575	325	250	26	193	324	32
16	DIMBOVITA	142	78	64	14	73	50	5
18	GALATI	183	97	86	9	57	103	14
19	GIURGIU	73	43	30	0	28	33	12
20	GORJ	212	105	107	0	55	134	23
22	HUNEDOARA	288	175	113	0	137	130	21
23	IALOMITA	70	33	37	3	40	24	3
24	IASI	807	475	332	85	265	383	74
25	ILFOV	135	70	65	12	63	52	8
26	MARAMURES	312	170	142	3	85	198	26
27	MEHEDINTI	1	1	0	0	0	1	0
28	MURES	437	239	198	33	183	183	38
31	PRAHOVA	150	83	67	2	64	76	8
32	SATU-MARE	56	28	28	0	20	29	7
33	SALAJ	88	63	25	1	31	44	12
34	SIBIU	395	213	182	15	159	203	18
35	SUCEAVA	329	183	146	7	146	144	32
36	TELEORMAN	151	131	20	0	14	78	59
37	TIMIS	100	46	54	7	31	53	9
38	TULCEA	30	13	17	0	11	16	3
39	VASLUI	155	80	75	1	59	81	14
40	VILCEA	61	36	25	0	36	24	1
41	VRANCEA	4	2	2	2	0	2	0
42	BUCURESTI	592	301	291	54	265	251	22
	TOTAL	7634	4205	3429	399	2838	3808	589
	%	100%	55.08%	44.92%	5.22%	37.17%	49.88%	7.71%

TABLE 1. Other muco-cutaneous viral infections: reports from general practitioners in 2012 (source: National Center for Statistics and Informatics in Public Health).

groups were 0-20 years, 21-65 years and over 66 years. All statistics was performed using Microsoft Office Excell 2003. □

RESULTS

In the general population (males and females combined) the total number of EGW cases registered by the hospital departments of Dermato-venereology databases was of 266 for the year 2012 (Table 3), representing only 0.8% from the total number of consultations. Most cases were registred in Constanta (128 cases) followed by Colentina Hospital Bucharest (50 cases) and Timisoara (47 cases). The sex distribution is showing a male preponderance with a total of 147 male cases versus 119 female cases. From all age groups analysis, only in the 15-20 year-age group the female cases out-

numbered the male patients. There were no cases reported for the age group 0-1 year. The regional distribution indicates a higher number in urban cases (175 patients; 65.8%) when compared to rural cases (91 patients; 34.2%). The main difference was registered in Bucharest with 42 patients from urban areas versus 8 patients from rural areas. □

DISCUSSIONS

Genital infection with HPV occurs most commonly by intimate contact with individuals who harbor clinical or subclinical HPV lesions, with transmission rates of 60% between partners (5). Transmission of HPV is enhanced when the superficial epithelium is disrupted (6). Evidence of infection with the high risk oncogenic HPV 16 and 18 genotypes, can be

Romanian County / Hospital	TOTAL EGW 2012	EGW as first diagnosis	EGW as secondary diagnosis	Male patients	Female patients
ALBA	12	0	12	0	12
ARAD	21	4	17	3	18
ARGES	18	7	11	7	11
BACAU	13	1	12	0	13
BIHOR	26	18	8	7	19
BISTRITA-NASAUD	5	2	3	1	4
BOTOSANI	35	1	34	0	35
BRAILA	23	3	20	1	22
BRASOV	14	2	12	2	12
BUCURESTI	118	37	81	52	66
BUZAU	18	1	17	0	18
CALARASI	16	11	5	8	8
CARAS-SEVERIN	31	10	21	2	29
CLUJ	25	5	20	9	16
CONSTANTA	32	4	28	7	25
COVASNA	9	2	7	0	9
DIMBOVITA	21	3	18	2	19
DOLJ	49	28	21	19	30
GALATI	37	3	34	3	34
GIURGIU	9	0	9	0	9
GORJ	26	22	4	12	14
HARGHITA	20	9	11	1	19
HUNEDOARA	38	9	29	6	32
IALOMITA	5	0	5	0	5
IASI	55	11	44	19	36
ILFOV	6	2	4	3	3
MARAMURES	5	4	1	3	2
MEHEDINTI	32	8	24	7	25
MURES	36	4	32	2	34
NEAMT	17	2	15	5	12
OLT	5	2	3	1	4
PRAHOVA	42	3	39	1	41
SALAJ	1	1	0	0	1
SATU MARE	3	2	1	2	1
SIBIU	6	2	4	3	3
SUCEAVA	21	4	17	2	19
TELEORMAN	13	9	4	8	5
TIMIS	32	10	22	12	20
TULCEA	9	6	3	6	3
VASLUI	28	5	23	2	26
VILCEA	9	0	9	0	9
VRANCEA	11	4	7	3	8
TOTAL	952	261	691	221	731
%	100%	27.4%	72.6%	23.2%	76.8%

TABLE 2. External genital warts (EGW) reported from the Romanian hospitals in 2012 (data from the National School of Public Health, Management and Professional Development).

found in up to 70% of squamous cell carcinomas of the cervix (7). Genital warts are caused in 90% of cases by infection with HPV types 6 and 11 (8). About 46% of women will experience cervical HPV infection within 3 years of initiating sexual activity, with a median time of 3 months between first sexual intercourse and the first detection of HPV (9).

Behavioral risk factors for infection include sexual intercourse at an early age (in sexually active individuals 15–24 years of age (10)), the number of lifetime sexual partners, the partner's number of sexual partners (11,12). Additional risk factors include unprotected intercourse, use of oral contraceptives, a history of

sexually transmitted infections or immunosuppression (13,14). Individuals who smoke are more likely to develop cancer (15). HPV co-infection with Herpes Simplex Virus 2 or with Chlamydia trachomatis increases the risk for squamous cell carcinoma of the cervix (16,17).

All the present therapies only destroy the lesions, without clearing the virus, so most of the lesions recur. That is the reason why prevention of infection with HPV is very important. Two prophylactic HPV vaccines are now available. Both target HPV types 16 and 18, and one of the vaccines also targets HPV types 6 and 11. The quadrivalent HPV recombinant vaccine (covering types 6, 11, 16, 18.) was approved in

	Total consultations 2012	2012																
		total	Female (F)	Male (M)	1-14			15-20			21-65			+65			Rural areas	Urban areas
					total	F	M	total	F	M	total	F	M	total	F	M		
Bucharest	17521	50	15	35	1	0	1	6	5	1	43	10	33	0	0	0	8	42
Constanta	1826	128	75	53	4	3	1	8	5	3	115	67	48	1	0	1	49	79
Craiova	6957	19	8	11	2	2	0	10	5	5	6	1	5	1	0	1	9	10
Targu Mures	5597	22	9	13	0	0	0	2	2	0	20	7	13	0	0	0	6	16
Timisoara	4408	47	12	35	3	1	2	1	0	1	43	11	32	0	0	0	19	28
Total	30712	266																
119	147	10	4	6	27	17	10	227										
96																		
132	2	0	2	91	175													
%		100%	44.7%	55.3%	3.7%			10.1%			85.3%			0.9%			34.2%	65.8%

TABLE 3. External genital warts patients registered in 5 Romanian Dermato-Venereology Clinics.

2006 in USA. Three doses of 0.5 mL of the tetra-valent vaccine are administered intramuscularly at day 1, month 2, and month 6 (18). The results of the FUTURE I study shows that the prophylactic quadrivalent HPV vaccine is highly effective in preventing clinical disease, including ano-genital warts and intraepithelial neoplasia of the cervix, vagina, and vulva (19). It is indicated for girls and women as young as 9 years (but typically given at 11 years) to 26 years. A bivalent vaccine that protects against the two major serotypes that are involved in cervical cancer (HPV types 16 and 18) was also produced. Currently, the American Cancer Society recommends routine vaccination for all females beginning with 9 years of age up to 26 years of age and for all males from 9 years of age up to 21 years of age (20).

In the data reported by the general practitioners and in the data reported by the hospitals at national level, the cases of EGW are seen more frequent in females: NSPHMPD data showing 76.8% females with EGW and 23.2% males with EGW. In our study from the Dermato-venereological departments there was a slim majority of males. It is possible that the females with HPV infection have a bigger addressability to gynecologists and also that they have asymptomatic infection. The HPV infection seems to be more frequent in the urban areas but this situation is created by the social life and sexual habits in the cities.

The presence of EGW is embarrassing for most of the patients, therefore they prefer to refer to the private clinics, rather the departments of Dermato-venereology of the public hospitals. This data is clear shown in Timisoara and Constanta where the number of patients registered at the single Emergency room in

town is greater than the number of patients reported by the NSPHMPD suggesting that some patients chose to have their treatment in other medical facilities. An additional factor can be the low interest of hospital doctors to treat EGW as in-patients due to the low Case Mix Index (CMI). Most of the EGW reported to the NSPHMPD had EGW as a secondary diagnosis.

Worldwide the EGW reported annual incidence rates typically range between 100 and 200 new cases per 100,000 general adult population based on retrospective administrative databases, medical chart reviews and prospectively collected physician reports (21). In Bucharest, in 2012 there were reported to NSPHMPD only 118 cases (50 patients being reported by the main dermatological unit in the city) at a general population of 1,900,000. The same situation is encountered in the third most populated Romanian town – Timisoara – with 32 cases reported by NSPHMPD (47 patients presented at the local hospital Emergency Room) for a general population of 320,000. Those data are demonstrating the low frequency of patients with EGW presenting for dermato-venereological consult. The untreated patients are at risk to develop complications and also are responsible for the spread of the infection. These cases represent a public health concern and HPV medical information (e.g. leaflets for patients, internet announcements) must be spread in the general population. A reliable electronic system for reporting the HPV cases would permit also contact notification and would decrease the total number of infected persons.

The general costs involved in the management of HPV patients is high due to: (i) the recurrence of the disease, (ii) its complications

(e.g. cervical cancer), (iii) asymptomatic viral shedding and (iv) increasing number of new cases.

For the year 2012 Romania was on the first place with the biggest estimated frequency of cervical cancer incidence (Estimated age-standardised rate (European standard) (ASR) = 34.9) and mortality rate (ASR: 14.2) in a list of 40 European countries (22). For the year 2008 the situation was the same (23).

The logical step to reduce these costs is to increase the awareness of the public on this disease. Among the necessary medical measures, adding the HPV vaccine to the national vaccination programs, seems a useful preventing one. The authors recommend the use of the tetravalent vaccine. The HPV vaccination is effective if it is performed before the beginning of the sexual life. Due to the increase of the incidence of cervical cancer the HPV vaccination was mainly promoted for girls. Boys can also benefit from the vaccine (age recommendation 11-12 years) as there is a high prevalence of anal, penile and oro-pharyngeal cancer in males, in which HPV has been proven to have a role (24). The authors support the vaccination in boys for reducing the number of cases with HPV induced oral or genito-anal cancer but also for the decrease of the total number of persons infected by HPV (the reduction of the infected cohort). □

CONCLUSIONS

The high contagiousness of genital HPV infection, the role this virus has in the induction of cervical dysplasia and the high incidence of cervical cancer in our country represent significant public concerns. Our study proved that in the case of HPV infected patients there is a big discrepancy between data collected by dermato-venereologists in five important tertiary referral units and data collected by NSPHMPD or reported by the general practitioners. Those reports need to use the same coding system. An improved electronic system for medical data collection may bring to light the real situation and would permit the identification of needed steps to reduce the incidence of the HPV infection and its co-morbidities. The high incidence of HPV infection in young persons living in urban areas, revealed by our study, supports the importance of awareness messages that must be transmitted with high priority to this group: firstly, the risk they have by engaging unprotected intercourse and secondly the benefits of the vaccination, for both girls and boys. The tetravalent vaccine prevents infection with the HPV types that produce external genital warts (6 and 11) and with those types more frequently involved in the induction of cervical cancers (16 and 18).

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