

Cervical Cancer Control in Romania Requires Optimization

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ABSTRACT

Background: Romania is recognized by GLOBOCAN 2012 being on the top of the first 20 countries in UE, regarding mortality through cervical cancer. Cervical Cancer Action mention Romania having a national program for HPV vaccination, but in the same time there is not mentioned any HPV DNA testing program in this country. In this paper we want to present the results of HPV genotyping in different categories of Romanian women, from different region of the country, being at risk for cervical cancer developing: patients with Pap abnormalities, women tested after LEEP and HIV positive women.

Analysis: we analysed 11 articles published between 1998 – 2016. The most frequent technique used for HPV genotyping was Linear Array. The detected high risk HPV prevalence in different regions of Romania varied between 22.6 – 64.3%.

Conclusion: the analysed studies support the required implementation of the organized screening of cervical cancer in Romania.

Keywords: HPV, Cervical Cancer, Screening, Risk Factors, HIV, Conization

INTRODUCTION

Human papillomavirus (HPV) is the necessary cause of cervical cancer, and also causes anal, vaginal, vulvar, penile, and oropharyngeal cancer. Romania is recognized by GLOBOCAN 2012 being on the top of the first 20 countries in UE, regarding mortality through cervical cancer (10.8 / 100 000) [1].

In 2012 it was a Romanian governmental attempt to implement national HPV vaccination programme of two human papillomavirus (HPV) vaccination programmes: Cervarix and Gardasil. These two first-generation, U.S. Food and Drug Administration (FDA)-approved vaccines prevent infections and disease caused by HPV16 and HPV18, the two HPV genotypes that cause approximately 70% of cervical cancer, and one of these vaccines also prevents HPV6 and HPV11, the two HPV genotypes that cause 90% of genital warts. Data regarding efficacy, cost-effectiveness, and safety, universal HPV vaccination of these two first-generation are published in systematic reviews, and more than this, there are data regarding vaccine efficiency for the new generation vaccine which target five additional HPV genotypes that together causes approximately 90% of cervical cancer as well as HPV 6 and HPV 11 [2,3].

Now, after for years since then, the uptake of HPV vaccine in Romania remained extremely low and the programmes were discontinued. The possible explanation for this failure can be related to three factors: quality of information given to general population, way of transmission of these data and the medical knowledge of general population and also of some part of medical staff.

Regarding the quality of information, one article mention that negatively disposed reports were more likely to contain incorrect data about vaccine efficacy and less likely to provide comprehensive information about the vaccine and HPV-related diseases. The methods used to spread information regarding HPV vaccination were newspapers, magazines, videos and informational websites published online. Regarding the vaccine acceptability in general population, the most dominant vaccine-related concerns were side effects and insufficient testing. Another category of women backed up their rejection of participation in official reproductive care programmes by mentioning 'God's will' as the ultimate trigger of cervical cancer. These data suggest that educational interventions are greatly needed as a response to suboptimal and incomplete media coverage of HPV vaccination [4,5].

Beside educational interventions it will be necessary to mobilize local political will. Political commitment and advocacy must be sufficiently strong to sustain good policies and programmes. Romania should be urged to build strong support for investment, to make concerted use of the mass media and create supportive legislative and regulatory framework.

Cervical cancer can now be prevented. Organized, population-based screening and vaccination programmes are complex and expensive undertakings that will not be implemented without substantial political support to set national healthcare priorities, implement the required policies and approve the required budget.

Romania was known, till recent, having no data regarding HPV genotype presence in case of precancerous lesions (ASCUS, ASCH, LSIL, HSIL) or in case of cervical cancer [6]. It is worldwide recognized that HPV is the necessary condition for cervical cancer, so it would be logical that prevention strategy to implement in this country a national screening protocol for HPV DNA testing.

The aim of this chapter is to analyse the studies performed in Romania regarding HPV prevalence in different categories of women, like a proof for required of organized screening of cervical cancer.

ANALYSIS

We analyzed 11 article which published their results regarding HPV prevalence between 1998 - 2016. In the Table I we present the women category which was tested, the genotyping method used and the result of HPV prevalence.

HPV / DNA Assays

The studies performed by Romanian authors used kits for complete HPV genotyping (Linear Array or INNO LiPA), except two of them which used in situ hybridisation [10,17]. The prevalence of HR HPV types detected was between 22.6 – 64.3%, according with the category of tested women: with normal / abnormal Pap test, with CIN (cervical intraepithelial neoplasia), after loop excision procedure as treatment of cervical dysplasia, or HIV positive women.

For our knowledge, these studies were possible thanks to some regional grants research, or were performed in the private laboratories. This explain the low number of studies published. Also we should underline that only a small proportion of women were invited to participate in the grant supported studies, or only the ones which afforded to pay the genotyping analysis in the private laboratories. This is characteristic for opportunistic screening of cervical cancer, which is known that is not having a wide coverage. Another drawback of opportunistic screening is that the quality control of testing is in related with the local laboratory, with the professional experience, with or without monitorization of quality control. By comparison, the organized screening suppose a wide coverage due to the sistem „call – recall”, which assure that all the women are included in the program. Also different is the quality control which is made at the central level, with periods of training and periodic audits.

Worldwide there are many HPV tests available: kits for HR HPV detection (HC2, Cervista), DNA/HPV testing with simultaneous HPV partial genotyping (Cobas 4800 HPV, Roche, Real Time PCR HR HPV, Abbot), or with complete HPV genotyping (Linear Array, INNO-LiPA) and also kits for ARNm E6/E7 detection. Some of these tests are having FDA approval, or wide usage, but only a few of them are clinically validated.

For primary cervical cancer screening, from the multitude of available tests, should be used validated assays which assure high-quality screening. The criteria used to evaluate clinical

validity are based on reproducibility and relative sensitivity and specificity compared to Hybrid Capture-2 or GP5⁺/6⁺ PCR-enzyme immunoassay [18].

In case of Romanian HPV studies, even an author has obtained WHO proficiency for HPV genotyping using Linear Array HPV Genotyping test [15], none of the used test belongs to the clinical validated tested like Hybrid Capture-2, GP5⁺/6⁺ PCR-enzyme immunoassay, cobas 4800 HPV test or Abbott RealTime High Risk HPV, established by Arbyn M et al. [17]. It would be useful that in Romania to be more companies which should offer HPV assays. This will give the opportunity to choose the best test, from analytical and financial point of view. The recent VALGENT framework study extended current guidelines for high-risk HPV test validation in cervical cancer screening, in collaboration with WHO reference laboratory network. The idea is to assess clinical HPV methods starting from sampling procedure, handling the specimens till analytical accuracy [19].

Table 1: The HPV prevalence detected in different Romanian regions.

Author, region of Romania	Year of publication	Women category	HPV genotyping method	Detected HPV prevalence
Ursu RG [7], North East	2016	After LEEP	Linear Array	22.6% HR HPV
Ene L [8], South	2015	HIV positive HIV negative	Linear Array	28/65 (43.1%) DNA/HPV 21/65 (32.3%) HR HPV 8/25 (32.0%) DNA/HPV 6/25 (24%) HR HPV
Ursu RG [9], North East	2015	HIV positive HIV negative	Linear Array	18/40 (45%) DNA/HPV 350/992 (35.2%) DNA/HPV
Ancuța E [10], North East	2013	Cervical cancer	in situ hybridization	100 % HPV 16 and/or 18
Moga MA [11], Center of country	2014	Normal / Abnormal Pap	35 HPV types	48.2% HR < 3% LR
Stănculescu R [12], South	2013	22 ASC-US 41 LSIL	Linear Array	41% ASC-US HR 51.2% LSIL - HR
Melinte-Popescu A [13], North East	2012	CIN	Linear Array	57.23% DNA/HPV
Feticu L [14], West	2012	Normal / Abnormal Pap	INNO-LiPA Linear array	54.4% HPV
Ursu RG [15], North East	2011	Normal / Abnormal Pap	Linear array	192/514 (37.4%)
Anton G [16], South	2011	Normal / Abnormal Pap	INNOLiPA	279 (60.7%)
Virtej P [17], South	1998	CIN	dot-blot hybridization	18/ 28 (64.3%) HPV16 , 11/ 28 (39.3%) HPV18 6/28 (21%) HPV 16/18

Category of Tested Patients

HPV/DNA testing, like a secondary screening test, can be used for triage of women with cytologic anomalies, for a combined screening (cytology and HPV testing) or can be used for monitoring of treated women.

The most of the analysed articles tested women with normal Pap test or with different cytologic abnormalities of Pap smear, or in case of women which never tested for Pap smear.

Regarding the region in which were performed the studies, we can say that they covered all the country. But we should mention that we lack organization of testing women for screening, using for example, regional registries of precancerous cervical lesions. We could use, like a model the nation-wide programmes for cervical cancer screening in the Nordic countries, which started the screening many years ago (e.g., Denmark – 1962, Norway – 1995). In these countries are offered detailed information of the coverage (between 23 - 100 %), recalls, the target ages (between 20 – 75), screening interval (between 3-5 years).

Two of the selected articles have tested HIV positive women. This is a particular category of patients which were iatrogenically infected at birth [8,9] Both articles found an increased HPV prevalence in case of HIV positive women, even they were under HAART therapy. Another team tested only patients diagnosed with cervical cancer which explain the fact that all the women were positive with HPV 16 and/or 18 [10]. Another study evaluated the HR HPV prevalence after LEEP and the persistent infections were with 16, 18, 31, 39, 51 and 66 HPV types. Univariate analysis found that age over 30 years, multiparity, use of contraception and CIN2-3 were significant factors for persistence of HR-HPV after LEEP [9].

CONCLUSIONS

Scientific data is essential but it is not enough. Without political support, these large-scale public health programmes will not be implemented. These 11 studies are just a few, but they are the proof that HPV can be detected in a correct manner. We should use these information to follow-up women with CIN, in order to prevent evolution to cervical cancer. Cervical cancer prevention programmes are large and complex undertakings that will not be implemented without substantial support. Obtaining political support should be obtained from politicians which entered politics because they wanted to improve the societies in which they live. Few of them have any knowledge of cervical cancer, its impact on society or what can now be done about it. Educational programmes should target the general public, healthcare professionals, the media and politicians.

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