RESULTS OF PRIMARY PREVENTION IN CERVICAL CANCER. ANTI-HPV VACCINATION. UPDATE OF FIGO CLASSIFICATION IN CERVICAL CANCER (2018)

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Abstract: *Cervical cancer is considered a major public health problem, 90% of deaths due to this neoplasia occur in the developing countries. Cervical cancer is the second type of cancer diagnosed in the genital cancers' hierarchy and the third cause of death due to cancer among the female population. In Romania, the incidence of cervical cancer and the mortality caused by this type of cancer is increased. In 2018, Globocan reports a number of 3308 newly diagnosed cases of cervical cancer in Romania. HPV infection is the main cause (99%) of cervical tumours and neoplastic precursor lesions, being also a sexually transmitted disease. Therefore, primary prevention programmes (HPV vaccination, immunization) and secondary prevention - cervical cytology screening, co-tests - primary HPV phenotyping and immunocytochemistry - histochemical biomarkers detection have been implemented worldwide. It is important to emphasize the results reported in 2018, of huge importance for the general population health, implemented by Australia, through the National Vaccination Programme, with quadrivalent vaccine (4v HPV 6,11,16,18), initiated in 2007 for female sex and extended since 2013 to the male sex. Conclusion of the Australian National Vaccination Programme: viral removal and eradication of HPV disease, thus demonstrating the efficacy and feasibility of the primary prevention programme.*

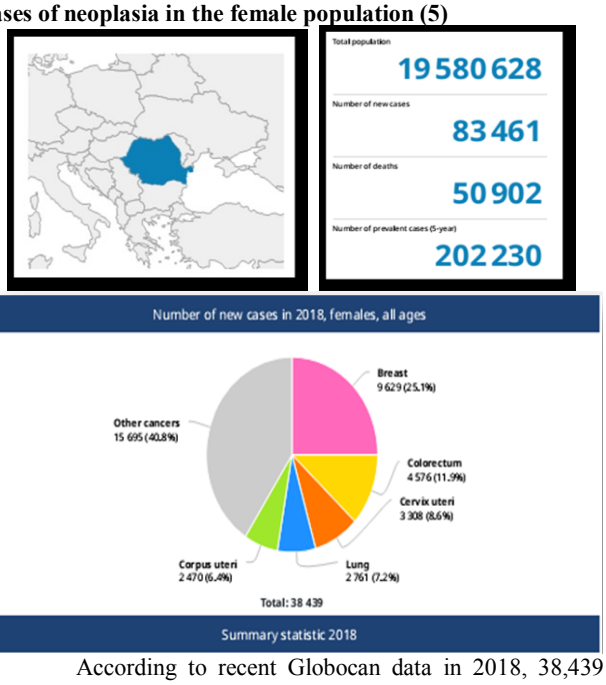
Cervical cancer is the second type of cancer diagnosed in the genital cancers' hierarchy and the third cause of cancer due to death among the female population.(1) According to the World Health Organization (WHO), around 500,000 women with cervical cancer are newly diagnosed throughout the world, 200,000 of which die from this disease.(2)

Cervical cancer is considered a major public health problem, as approximately 90% of deaths due to this neoplasia occur in the developing countries, with a net geographical variation between the developed and developing countries. The variation is explained by the presence of 3 common elements in developing countries: increased prevalence of Papilloma Human (HPV) infections following a liberal attitude regarding the sexual practices (HPV infection being considered a sexually transmitted disease) and lack of implementation, low accessibility or ineffective screening (diagnosis, therapeutic sanction and suboptimal follow-up of precancerous cervical lesions).(3)

ESMO clinical guidelines on cervical cancer also points to this variation, which is based on the complication of the three factors mentioned above, also showing a survival rate of 5 years for women diagnosed with cervical cancer in Europe during 2006-2007, on average of 62%, with the following indications: in the North of Europe, 67% increase in the 5-year survival rate (in Norway even an increase of 71%), while Eastern Europe is diametrically opposite with a survival rate of 57% (particularly low <55% in Bulgaria, Poland, Latvia).

In Romania, unfortunately, the incidence of cervical cancer and the mortality caused by this type of cancer is increased.(3) Globocan reported in 2008 that the incidence of cervical cancer in Romania was 23.9 / 100.000 women, and the mortality rate was 11.8 / 100.000 women.(4)

Figure no. 1. Romania 2018, statistics on newly diagnosed cases of neoplasia in the female population (5)



According to recent Globocan data in 2018, 38,439 new cases of cancers in the female population in Romania were diagnosed, cervical cancer representing 3,308 cases (8.6%).(5)

Currently, it is widely accepted and demonstrated by virology and molecular biology studies that HPV infection is the main cause (99%) of cervical tumours or neoplastic precursor lesions.

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We note that of this 99% percentage of HPV infections, 80% are transient (mostly in the 24-year-old female population, adolescents) and the rest are persistent (especially with the high oncogenic strains of type 16 and 18 of all 14 oncogene stems), creating the premise according to the lesional continuity theory with the turning of dysplastic lesions to neoplasia, especially in the female population aged 30 years and over, which often also presents accumulations of genomic alterations in the somatic cells (representing a factor contributing to tumorigenesis) that make them more susceptible to infection or malignant transformation.

This is why primary prevention (anti-HPV vaccination, immunization) and secondary prevention programmes have been implemented worldwide - screening cervical cytology, classically or in liquid environments to which co-tests have been added - primary HPV phenotyping and immunocytosis -/- histochemical detection of some biomarkers from cytoscopy and biopsies obtained as a result of colposcopy, direct biopsy of a suspected lesion or on parts obtained after surgical treatment

In specialty bibliography, post-implementation of vaccination programmes of about one decade with bivalent/ quadrivalent/ new-valent licensed vaccines have been reported, as well as significant decreases in the incidence of genital warts, cytological results such as high-grade intraepithelial precursors, HPV associated cancers in women (table no. 1) and in men. We mention that in the USA, Australia - a prophylactic vaccination programme against HPV and the male population was initiated.

Postimmunization, there have been reported annual reductions in the incidence of the following types of HPV related neoplasia: 90% - cervical cancer, 92% - anal cancer, 87% - vulvar cancer, 85% - vaginal cancer, 85% - penile cancer. Through these significant decreases, with a strong impact on reducing the incidence of cancer related to HPV infection, it results that due to vaccination, a good primary prevention has been obtained through the vaccination programme, respectively by immunization (with either prophylactic or therapeutic valence) (table no. 2).

It is important to emphasize the results reported in 2018, of huge importance for the general population health, implemented by Australia, through the National Vaccination Programme, with quadrivalent vaccine (4v HPV 6,11,16,18), initiated in 2007 for female sex and extended from 2013 to male sex. Conclusion of the Australian National Vaccination Programme: viral deletion and eradication of HPV disease, thus demonstrating the efficacy and feasibility of the primary prevention programme.

Table no. 1. Result of Vaccination and Prevalence of HPV Genital Infections in the 18-24 age group (6)

Estimates of genital HPV prevalence among sexually active women aged 18–24 years, by HPV type, Australia, 2005–2012 (n = 1,260)

HPV type	Pre-vaccination era (2005–07) (n = 202)	Post-vaccination era (2010–12) (n = 1,058)		
	Overall population prevalence	Overall population prevalence	Prevalence in vaccinated	Prevalence in unvaccinated
HPV 6	5.5%	0.9%	0.2%	2.7%
HPV 11	1.5%	0.4%	0%	1.3%
HPV 16	21.3%	4.2%	1.5%	12.1%
HPV 18	8.4%	1.9%	0.6%	7.4%
HPV 31	5.0%	4.0%	2.7%	8.1%
HPV 33	4.0%	1.5%	1.4%	2.0%
HPV 45	1.0%	2.6%	1.7%	6.0%
HPV 52	7.4%	8.2%	6.9%	9.4%
HPV 58	5.5%	3.4%	3.9%	2.7%
HPV 6/11	6.9%	1.3%	0.2%	4.0%
HPV 16/18	26.2%	5.4%	2.1%	16.1%
HPV 31/33/45	9.4%	7.8%	5.6%	14.8%
4vHPV types[a]	28.7%	6.5%	2.3%	18.8%
High-risk HPV types[b]	47.0%	34.9%	34.4%	44.3%
All HPV types	59.9%	48.8%	49.4%	55.7%

HPV: human papillomavirus.

Data were obtained from Figure 1 and Table 4 of a paper reporting results of the Vaccine Impact in the Population study, where cervical specimens were obtained from women attending family planning clinics in three states [18]. Overall prevalence data were calculated manually using the information in Table 4 of the original publication.

[a] 4vHPV types include HPV types 6, 11, 16 and 18.

[b] High-risk types include HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68.

Table no. 2. The link between HPV strains and high-grade cervical lesions, respectively cervical cancer (6)

Proportion of cervical disease attributable to vaccine-targeted HPV types, Australia

HPV type	High-grade cervical abnormalities[a]	Cervical cancer[b] (95% CI)	HPV-positive cervical cancer[c] (95% CI)
16	51–60.3% [20,70-72]	51.6% (48.2–55.0)	56.0%
18	5–13% [20,70-72]	19.6% (17.0–22.4)	21.5%
31	11–15.8% [20,70,72]	2.5% (1.5–3.8)	2.7%
33	7.8–11% [20,70]	4.3% (3.0–5.8)	4.6%
45	3.0–6.4% [70]	5.0% (3.6–6.6)	5.5%
52	11.2–18.1% [20,70]	2.4% (1.4–3.6)	2.5%
58	5.8–8.8% [70]	0.6% (0.2–1.4)	0.6%
16/18	57.2–65.7% [20,70-72]	71.8% (68.5–74.7)	77.1% (74.0–80.0)
31/33/45/52/58	Unknown	14.8% (12.4–17.3)	15.9% (13.4–18.6)
9vHPV types	Unknown	86.4% (83.9–88.7)	93.0% (91.0–94.7)

CI: confidence interval; HPV: human papillomavirus.

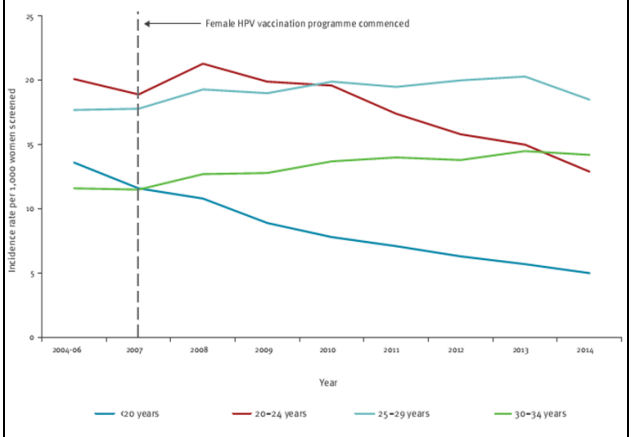
[a] Includes: Adenocarcinoma in situ and cervical intraepithelial neoplasia grade 2 or 3.

[b] Obtained from the Australian Cervical Cancer Typing Study (ACCTS) [40]. These data are for all cervical cancers typed (n=847). HPV was not detected in all specimens, which may be due to failure of detection following integration of HPV DNA, assay failure, misclassification of uterine cancers as cervical cancer or rarely to true HPV-negative cancers.

[c] Obtained from the Australian Cervical Cancer Typing Study (ACCTS) [40]. These data are for HPV-positive cervical cancers typed (n=787). The proportion of HPV-positive cervical cancers attributable to the individual 9vHPV types was calculated manually using data from Table 1 in Brotherton et al. [40]. As such, 95% CIs are not available for these proportions. The following formula was used, using HPV 16 as an example: [number of specimens with HPV 16 alone (single HPV genotype) + number of specimens with HPV 16 and other HPV types (multiple HPV genotypes)] / total number of HPV-positive cervical cancers.

Figure no. 2. Results of the National Programme of Anti-HPV vaccination by age groups (Australia)

Trends in high-grade cervical abnormalities in women by age group before and after commencement of the female HPV vaccination programme, Australia, 2004–2014



HPV: human papillomavirus.

Source: Australian Institute of Health and Welfare, 2016. Cervical screening in Australia 2013 to 2014 [25].

The successful strategies of the Australia's National HPV Immunization Program targeted the following key elements:

1. prevention of cancer and diseases - HPV is a priority of public health. The vaccination programme is feasible through optimal results obtained in terms of cost-effectiveness.
2. target population age: females before sexual life onset - aged 11-13, women of reproductive age and active sexual life - up to the age of 26. Male population included later in the programme, boys aged 12-15 years.
3. a National Anti-HPV Vaccine Programme (HPV 9v, 9 strains 6, 11, 16, 18, 31, 33, 45, 52 and 58) is planned in the future, with a more favourable extrapolated impact, especially on the age group of 30-34 years old, respectively implementing a gender-neutral program.

Recently (2018) FIGO has updated the Clinical Classification of Cervical Cancer with new features of IB status - IB3 and stage III, III C1 and C2 respectively. These clinical updates have the role of properly defining and classifying the disease, with a view to a fair and optimal multimodal therapeutic approach with implications for the patient's prognosis.

Table no. 3. Update of Clinical Staging of Cervical Cancer, FIGO 2018

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri[b]
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes[c]
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous edema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

When in doubt, the lower staging should be assigned.
[a]Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumor size and extent, in all stages.
[b]The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.
[c]Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. Example: If imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r, and if confirmed by pathologic findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented.
Source: Bhatla et al.[17]

Observing primary and secondary prevention, along with an annual gynecological clinical consultation, female population health can be improved, significantly reducing the number of cases in advanced stages, when the patient's vital prognosis is influenced.

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