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Cervical Lesions and Cellular Atypia in a Female Population from Transylvania

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Abstract
Introduction: The purpose of this study was to detect the types of the cervix lesions and to establish the correlations between age, environment of origin, diagnosis and gravity of the lesions. *Methods:* In the period 2009-2012, all cervical secretions from female subjects presented at Integrated Outpatient Unit, of the Clinical Hospital for Infectious Diseases, Cluj-Napoca, Romania were tested by Babeş-Papanicolaou examination. Babeş-Papanicolaou cytological smear was performed according to the 2001 Bethesda System criteria. *Results:* From 3153 cervical secretions (2736 female subjects from urban areas and 417 female subjects from rural areas) with age 10 - 87 years, 2899 (91.9%) smears (372 women from rural area and 2527 women from urban area) had normal appearance. Premalignant or malignant lesions (positive cases) were detected in 254 (8.1%) smears (45 (12.1%) cases from rural area, 209 (8.3%) cases from urban area). In the urban area, most positive cases were recorded in the age range of 45-54 years, while in the rural areas in the age range of 35-44 years. The multivariate logistic regression analysis showed that environment and age significantly influenced the occurrence of positive cases (OR=1.44 95% CI 1.02-2.02, p=0.04 for rural area, OR=0.71 95% CI 0.60-0.85, p<0.001 for age). The correlation between age and the degree of severity diagnosis (r=-0.09, p=0.14) was not significant. *Conclusions:* Cervical lesions detected through Babeş-Papanicolaou test in adult women are more common in the rural area.

Keywords: Cytological technic; Papanicolaou test; Neoplasia; Human Papillomavirus (HPV); Premalignant; Intraepithelial lesion

Introduction

The increased number of the cases with HPV (Human Papillomavirus) in Romania [1] requires screening; particularly with Babeş-Papanicolaou test as a value of the cytological evaluation in the epidemiological surveillance of the cervical lesions [2].

The Babeş-Papanicolaou test is used for early detection of the premalignant and malignant lesions of the cervix [3, 4], the endocervical and endometrial cellular atypia [5] and, secondly, the bacterial, parasitic, fungal and some viral sexually transmitted infections [6-11]. The test is also recommended in individuals vaccinated against HPV. The introduction in practice of the Babeş-Papanicolaou test was followed by a significant decrease in uterine cervical cancer incidence and mortality [12, 13].

The purpose of this study was to detect the types of the cervix lesions and to establish the correlations between age, environment of origin, diagnosis and gravity of the lesions.

Material and Method

Selection and Description of Participants

In the period 2009-2012, all female subjects presented with prescription for cervical secretions at Integrated Outpatient Unit, of the Clinical Hospital for Infectious Diseases, Cluj-Napoca, Romania were selected in the sample.

Method

We performed the Babeş-Papanicolaou test on stained smears (the screening method) which was interpreted in accordance with 2001 Bethesda System criteria [14]. Abnormalities (presence of premalignant or malignant lesions in cervix) will be considered positive cases in the following. Normal results (absence of premalignant or malignant lesions in cervix) will be considered negative cases.

Different types of lesions detected were coded according to severity, as follows:

NILM=0
ASCUS=1
AGC=1
LSIL=2
ASCH=3
HSIL=4
Carcinoma (scuamous, endocervical or endometrial)=5

Statistics

The statistical analysis of the investigated cases was conducted for comparing the environments of the two groups, in case of normal probability distribution. The Student test with equal or unequal variations was used, depending on the testing in advance of the variation with the Levene's test. The Kolmogorov-Smirnov test was used for testing the normal distribution. Where variables did not show a normal distribution, Mann-Whitney test was used for ranks comparison. For comparing environments of more than two samples in the case of the normal probability distribution, Anova test was used for a factor with the Scheffe correction. Where variables did not show a normal distribution the Kruskall-Wallis test was used for ranks comparison. To establish the correlation between two continuous quantitative variables; the Pearson correlation coefficient (r) was used, and for finding the correlation between two continuous categorical variables, the Spearman correlation coefficient (r) was used. The technique used for estimating the correlation between two or more quantitative variables was the linear regression. For multifactorial analysis, the GLM (General Linear Model) module (Anova multi-way) was used. To estimate the relationship between two qualitative variables, the Chi-squared test was used. To estimate the relationship between two or more variables, the dependent qualitative one, the quantitative or qualitative independent variables, logistic regression was used. The relative risks, the 95% Confidence Interval and the statistical significance of each parameter were presented. The materiality threshold for the tests used was considered $\alpha = 0.05$. Statistical calculations were performed by using SPSS 13.0 and Microsoft Excel applications.

Results

Of the 3153 Babeş-Papanicolaou smears performed in the patients included in the study, 2899 (91.9%) of smears (originating from 2527 women from urban areas and 372 women from rural areas) were found to be normal. Abnormalities (positive cases) were detected in 254 (8.1%) smears (209 urban cases and 45 rural cases). The percentage of positive cases in rural areas 10.8% was significantly higher than the percentage of positive cases in urban areas 7.6% ($p < 0.001$). Distribution of the cases by years and environment was presented in table 1.

Table 1. Distribution of positive and negative cases by years and environment

Year	Urban areas		Rural areas		p
	Positive	Negative	Positive	Negative	
2009	95	756	20	129	<0.001
2010	50	778	14	89	0.004
2011	46	664	8	116	0.99
2012	18	329	3	38	0.57
Total	209	2527	45	372	<0.001

The trend of frequency of positive cases was decreasing in time per total and also in female from urban and rural environments (Figure 1).

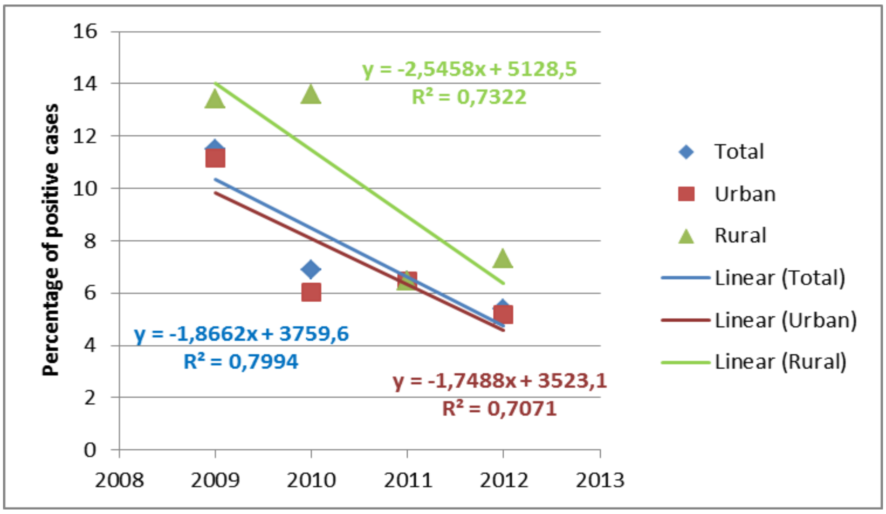


Figure 1. Trend for the frequency of the positive (pre-neoplastic lesions) cases in rural and urban areas over the time

Of the 3153 investigated cases, 156 (5%) cases had ASCUS (atypical squamous cells of "undetermined significance"), 63 (2%) cases had LSIL (low grade squamous intraepithelial lesion), 17 (0.5%) cases had ASC-H (atypical squamous cells "cannot exclude high-grade squamous intraepithelial lesion (HSIL)"), 13 (0.4%) cases had HSIL (high grade squamous intraepithelial lesion), 2 (0.06%) cases had AGC (atypical glandular cells), 1 (0.03%) case had AIS (adenocarcinoma in situ), 2 (0.06%) cases had squamous cell carcinoma.

Distribution of the number of studied cases by age, environment of origin and diagnosis in the period 2009-2012 was presented in Table 2 and in the Figure 2.

Table 2. Distribution of positive and negative cases by age, environment and diagnosis in the period 2009-2012

Years	Rural or urban areas	Positive or negative cases	Age (years)					
			≤ 24	25-34	35-44	45-54	55-64	≥ 65
2009	urban	positive	11	12	22	31	11	8
		negative	29	96	153	259	174	45
	rural	positive	3	3	4	9	1	-
		negative	5	24	41	39	18	2
2010	urban	positive	6	4	9	19	8	4
		negative	45	96	143	232	202	60
	rural	positive	2	2	7	-	1	2
		negative	5	18	29	21	13	3
2011	urban	positive	3	7	8	17	10	1
		negative	40	69	120	209	169	57
	rural	positive	2	3	2	1	-	-
		negative	8	20	36	32	18	2
2012	urban	positive	1	3	4	7	2	1
		negative	48	89	156	241	187	59
	rural	positive	-	-	1	2	-	-
		negative	-	5	18	7	8	-

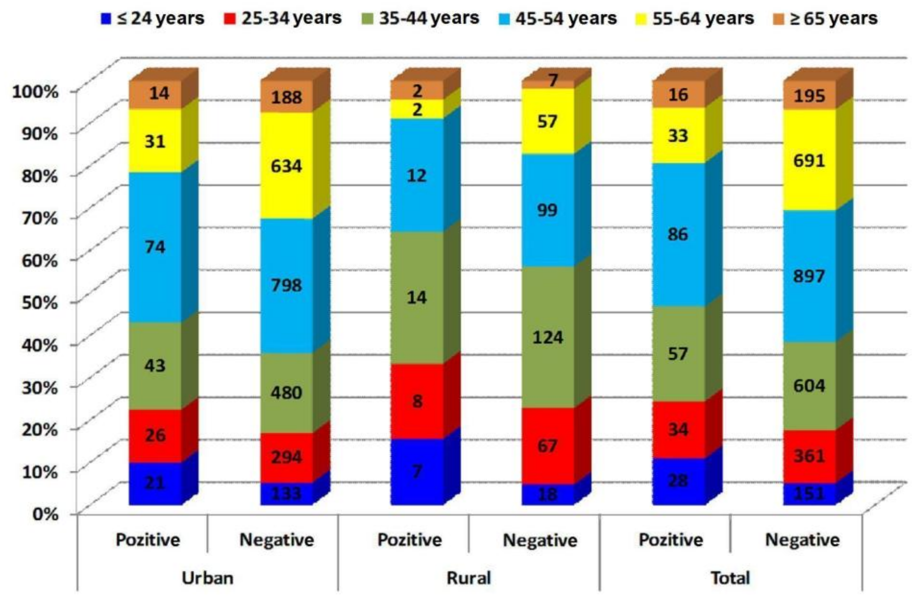


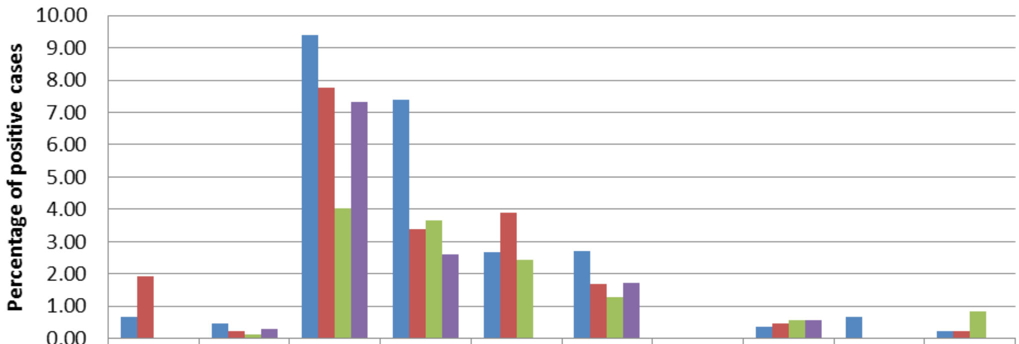
Figure 2. Distribution of the number of studied cases by age, environment of origin and diagnosis in the studied period

Multiway Anova – analysis of age shows that the average age was significantly different by environment ($p<0.001$) and by diagnosis (positive or negative) ($p=0.003$), but not significantly different by years of testing ($p=0.29$). The average age of women found positive was 44.35±13.23 years, as compared with the negative ones, which was 47.31±12.46 years, $p = 0.003$. The average age of women in urban area was 47.71±12.56 years, as compared to women in the rural area, which was 42.92±11.46 years, $p<0.001$. The average age in tested women was 46.57±12,18 years in 2009, 47.13±12.77 years in 2010, 47.32± 12.73 years in 2011 and 47.74±12.49 years in 2012 ($p=0.29$).

Of the 245 positive cases, 156 (61.4%) cases presented ASCUS (126 cases in urban area and 30 cases in rural area), 63 (24.8%) cases presented LSIL (52 cases in urban area and 11 cases in rural area), 17 (6.7%) cases presented ASC-H (14 cases in urban area and 3 cases in rural area), 3 (5.1%)

cases presented HSIL (in urban areas), 2 (0.8%) cases presented AGC (in a 29 years old woman from rural area, in 2009 and in a 55 years old woman from urban area, in 2010), 1 (0.4%) case presented AIS (in a 63 years old woman from urban area, in 2011), 2 (0.8%) cases presented squamous cell carcinoma (in a 44 years old woman in 2009 and in a 50 years old woman in 2010, both cases from the urban area).

The percentage distribution of positive cases according to the severity of diagnosis, years and environment is shown in Figure 3.



	ASC-H rural	ASC-H urban	ASCUS rural	ASCUS urban	LSIL rural	LSIL urban	HSIL rural	HSIL urban	other cases in rural	other cases in urban
2009	0.67	0.47	9.40	7.40	2.68	2.70	0.00	0.35	0.67	0.24
2010	1.94	0.24	7.77	3.38	3.88	1.69	0.00	0.48	0.00	0.24
2011	0.00	0.14	4.03	3.66	2.42	1.27	0.00	0.56	0.00	0.85
2012	0.00	0.29	7.32	2.59	0.00	1.73	0.00	0.58	0.00	0.00

Legend: other cases in rural: 1 case with AGC.
other cases in urban: 1 case with AGC; 1 case with AIS; 2 cases with squamous cell carcinoma.

Figure 3. The percentage distribution of positive cases according to the gravity of diagnosis, years and environment

Most cases were registered in urban areas, and the age range was 45-54 years, while in rural area the age range with the highest frequency of cases was 35-44 years. The smallest number of cases were identified in women with age over 65 years both in urban and in rural areas. The distribution of the cases with positive diagnosis, according to the degrees of severity of pre-neoplastic or neoplastic lesions, the environment of origin and the age groups in the period 2009-2012, was presented in Figures 4 and 5.

Bifactorial Anova – analysis shows that average degree of severity was not different according to the environment (p=0.28) and the years of testing (p=0.11).

Distribution of the average degree of gravity of the diagnosis by years and environment is shown in figure 6.

The correlation between the age and the degree of severity diagnosis, analysed using the Spearman correlation coefficient (r=-0.09, p=0.14) was not significant.

The multivariate logistic regression analysis shows that the environment (OR=1.44 95%CI 1.02-2.02, p=0.04), years of testing (OR=0.75 95%CI 0.65-0.85, p<0.001) and age (OR=0.71 95%CI 0.60-0.85, p<0.001) influenced the occurrence of positive cases. Rural environment suggests a risk of infection with HPV (Human Papillomavirus – showed through the presence of the koilocytes on the smear in positive cases) 1.44 times higher than in urban area. Positive cases decrease significantly in time and with age.

Of the 3153 investigated women, in 413 cases we found different sexually transmitted infections (table 3): 21 Trichomonas vaginalis infections (6 cases in rural areas), 158 cases with Gardnerella vaginalis (28 cases in rural areas), 167 cases of Candida spp (species pluralis) (23 cases in the rural area), 1 case of Chalamydia trachomatis (a woman of 52 years, urban area in 2011). We also found 31 cases with marked inflammation (5 cases in rural area), 21 cases with atrophy (2 cases in rural area), and 14 cases with koilocytes (LSIL) (2 cases in rural area) (table 4). Gardnerella vaginalis was found in 2009 in a 54-year-old woman of rural area who presented ASCUS; in the urban area, it was associated with ASCUS in a 24-year-old woman, in 2010 and in a 31-year-old woman, in 2011 (the other cases with Gardnerella vaginalis detected in rural and urban areas were NILM - negative for intraepithelial or malignant lesions). In the urban area, Candida spp. was found in a 26-year-old woman who had ASCUS, in 2011, the other cases of Candida spp. being NILM. All detected cases with Trichomonas vaginalis and Chlamydia trachomatis were NILM.

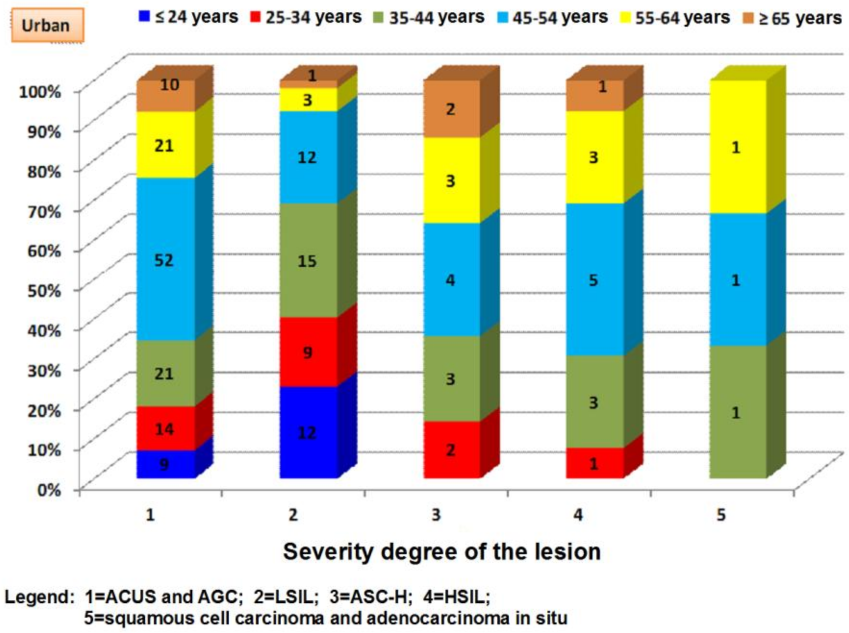


Figure 4. Distribution of cases with positive diagnosis by the degree of gravity of pre-neoplastic and neoplastic lesions, in the urban area and by age groups

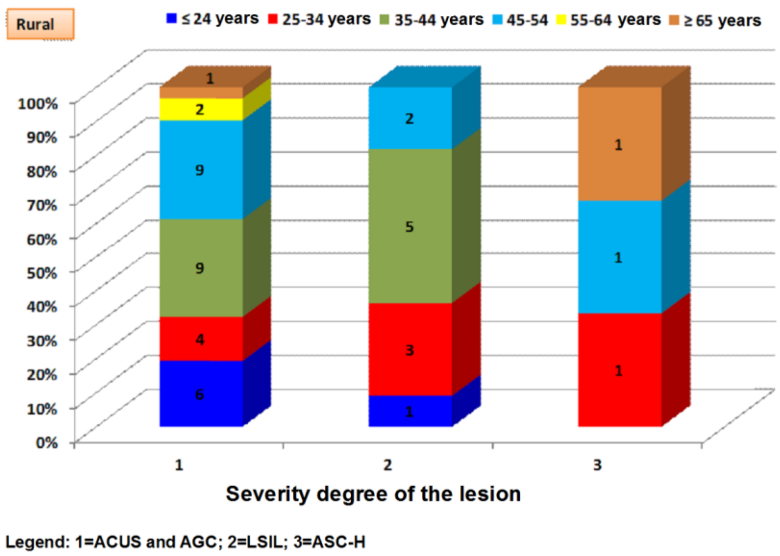


Figure 5. Distribution of cases with positive diagnosis by the degree of gravity of pre-neoplastic and neoplastic lesions, in the rural area and by age groups

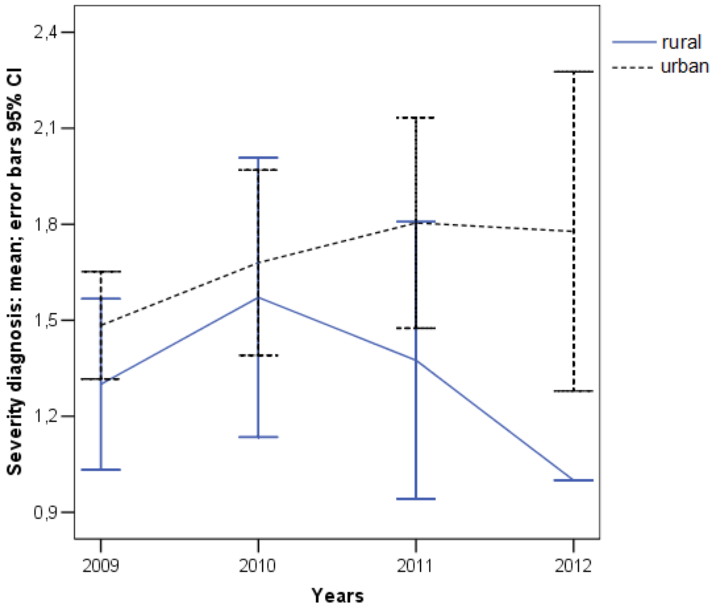


Figure 6. Distribution of the average degree of severity diagnosis by years and environment

Table 3. Distribution of infections and other changes found in women with Babeş-Papanicolaou smear by year, environment and age

Microorganisms and changes		2009		2010		2011		2012		Total	
		rural	urban	rural	urban	rural	urban	rural	urban	rural	urban
Trichomonas vaginalis	No.	2	2	1	5	2	6	1	2	6	15
	Age (years)	43; 52	40; 51	55	23-49	42; 47	24-65	40	26; 52	-	-
Chlamydia trachomatis	No.	-	-	-	-	-	1	-	-	-	1
	Age (years)	-	-	-	-	-	52	-	-	-	-
Gardnerella vaginalis	No.	9	29	8	43	11	47	-	11	28	130
	Age (years)	22-54	19-64	29-71	20-69	22-53	17-60	-	21-64	-	-
Candida spp.	No.	9	30	5	45	7	50	2	19	23	144
	Age (years)	25-57	20-71	27-43	19-67	20-53	23-71	36; 41	22-68	-	-
Marked inflammation	No.	-	-	1	8	2	13	2	5	5	26
	Age (years)	-	-	24	24-59	36; 37	30-73	47; 53	44-55	-	-
Atrophy	No.	-	4	1	5	-	5	1	5	2	19
	Age (years)	-	50-64	56	49-62	-	53-68	49	44-59	-	-
Koilocytes (LSIL)	No.	1	7	1	3	-	2	-	-	2	12
	Age (years)	46	20-56	34	21-26	-	21; 56	-	-	-	-

Discussion

The Babeş-Papapanicolau test is the standard method for detecting LSIL in women less than 35 years [15, 16]. If a high-quality cytological examination is used, the negative interpretation of the smears showing only signs of inflammation, results in a considerably lower positivity rate without increasing the risk of cervical cancer after assessing these smears as negative [17]. The Babeş-Papapanicolau test has a limited sensitivity; it needs to be repeated and causes high rates of false positives results [18]. Adding HPV detection to Babeş-Papapanicolau test for cervical cancer screening in women with an average age of 30 years reduced the incidence of 2 or 3 degree of cervical intraepithelial cancer detected by subsequent screening examinations [19]. Of the 3153 stained Babeş-Papapanicolau smears, 254 were positive for neoplastic or pre-neoplastic lesions. Similar results to those obtained in this study for detecting positive cases (ASCUS, LSIL, HSIL and squamous cell carcinoma) were also reported by other authors [20, 21, 22, 9]. The average age of the women with HSIL and LSIL in the present study is similar to those in other studies [9]. Similar results to those obtained in this study on the Babeş-Papapanicolau smears regarding squamous cell carcinoma and adenocarcinoma in situ were also obtained by other researchers [9].

In the same manner as in this study, other authors have highlighted within the stained Babeş-Papapanicolau smears the presence of inflammation [9], Trichomonas vaginalis [9, 10, 23], Chlamydia trachomatis [6, 24], Gardnerella vaginalis [9, 24], Candida spp. [10, 23] and the association of Candida spp. with ASCUS [22]. Some studies show that transient infections that can unleash cervical cancer are for example: the infection with herpes simplex virus type 2 [7], the infection with HPV [8] or with bacteria including Chlamydia trachomatis [8, 25-27]. Other studies did not found a relationship between Chlamydia trachomatis and cervical cancer [11, 28], the association between Chlamydia trachomatis and cervical pre-malignancy may be caused in part by an increased susceptibility to HPV infection [11]. In this study, only one case with Chlamydia trachomatis was detected. In contrast, some studies concerning Trichomonas vaginalis show that the virulent trophozoites may worsen or exacerbate conditions of cervical neoplasia [29].

Conclusions

This is the first study investigating the burden of pre-neoplastic and neoplastic cervical lesions assessed by Babes-Papanicolaou test in a feminine population in Transylvania in both urban and rural areas.

The frequency of the cervical lesions detected by the Babeş-Papanicolaou test is decreasing in time.

Cervical lesions detected by the Babeş-Papanicolaou test in adult women are more common in rural areas probably due to a better quality and better detection of patients addressing specialized medical care in urban areas.

The fact that women in the urban area with cervical lesions detected by the Babeş-Papanicolaou test were older than those in rural is somewhat paradoxical. It is difficult to correlate it with other risk factors - behavioral or medical - and requires further investigation.

The higher frequency of the cervical infections detected in the rural areas mirrors not just the better accessibility and addressability to health care in urban areas, but indirectly a higher sexual promiscuity and the need to improve sexual health education in rural areas.

List of abbreviations

AGC = atypical glandular cells;
AIS = adenocarcinoma in situ;
ASC-H = atypical squamous cells "cannot exclude high-grade squamous intraepithelial lesion";
ASCUS = atypical squamous cells of "undetermined significance";
HPV = Human Papillomavirus;
HSIL = high grade squamous intraepithelial lesion;
LSIL = low grade squamous intraepithelial lesion;
NILM = negative for intraepithelial or malignant lesions;
Spp = species pluralis.

Ethical Issues

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee.

Conflict of Interest

The author declares that he has no conflict of interest.

Authors' Contributions

LF carried out data collection, original concept, contribution to drafts, SIB provied scientific supervisor, original concept, contribution to drafts, CIB carried out statistical analysis, CB carried out literature review, contribution to drafts. All authors read and approved the final manuscript.

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