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Creation of risk index for premalignant changes of the uterine cervix

L.D. Tasic[1], L.G. Antic[2], A.I. Jursic[1], S.D. Jankovic[1], B. Kastratovic Kotlica[3], N.T. Karadzov[1], D.Z. Antic[2]

[1]University of Belgrade, Faculty of Medicine, Gynecology Obstetric Clinic "Narodni front", Belgrade
[2]Department for Medical Nurses-Midwives, College of Health Studies in Cuprija, Cuprija
[3]University of Belgrade, Clinic for Obstetrics and Gynecology, Clinical Center of Serbia (Serbia)

Summary

Objective: To construct a risk index for premalignant changes in the cervix uteri based on histopathological examination (HP) of biopsy of the cervix, in relation to demographic determinants, sexual behavior, and barriers for the implementation of preventive gynecological practice. *Materials and Methods:* The study included 525 patients; 90 had abnormal PAP test (ASC-US, L-SIL, H-SIL, and AIS). In 85 participants with unsatisfactory findings after colposcopy, targeted biopsy was performed. In 54 patients premalignant changes in the cervix uteri were found. The control group was represented by 31 respondents with benign changes in the cervix uteri. Distributions frequency of selected variables (socio-demographic and factors relating to the behavior associated with risk of cervical cancer) are shown in comparison to HP biopsy (benign / L-SIL, H-SIL, and CIS) and significance of the differences was tested by chi-square test. For a minimum level of statistical significance, $p < 0.05$ was used, while $p < 0.01$ was taken as statistically high significance. Variables that showed high significance after univariate logistic regression are further tested by multivariate analysis, and association is expressed through odds ratio and 95% confidence interval. *Results:* The authors presented factors that showed high statistical significance, making the risk model for development of malignancy on cervix uteri: the early onset of sexual activity, sexually transmitted diseases in the personal history, and the negative attitude in taking the Pap smear. *Conclusion:* The application of the model of risk index for cervical cancer would be helpful for doctors in primary healthcare in identifying women at increased risk, primarily in developing countries, such as Serbia.

Key words: Cervical cancer; Developing countries; Premalignant changes; Risk factors; Risk index.

Introduction

Serbia has a high incidence and mortality rate of cervical carcinoma. Cervical cancer represents a major public health problem [1]. Previous studies which have assessed the risk factors for cervical cancer were based on individual risk factors assessment [1]. Also, there are indexes relating only to the application of diagnostic methods [2, 3]. Some of the models are very complicated and hardly applicable in practice in underdeveloped and developing countries [4, 5]. These models relate to the application of diagnostic and therapeutic proceedings to provide more effective diagnosis and treatment of cervical cancer in early, but not during the invasive phase [6]. Diagnostic procedures that are applied for early detection of cervical cancer have limitations in terms of their sensitivity and specificity [7].

There is a need for a model that would be simple and convenient for usage in primary care in underdeveloped and developing countries. The implementation of such model would contribute to reducing potentially unnecessary procedures in prevention, diagnosis, and treatment, and would have the effect of reducing the costs in healthcare. In order to identify the women who are at risk for developing cervical cancer, it would be important to have one composite index. Several studies have shown the risk index for cervical cancer based on the Pap test [8, 9], but in diagnosis of cervical cancer, histopathological examination (HP) of biopsy specimens is the "gold standard" [10]. Therefore, in this study, the construction of the risk index for the assessment the incidence of cervical cancer is based on findings obtained by histopathological findings on cervical biopsy.

The objective to this study was to construct a risk index for premalignant changes in the cervix uteri based on HP result of targeted biopsy of the cervix, in relation to demographic determinants, sexual behavior, and barriers for the implementation of preventive gynecological practice.

Materials and Methods

Testing of risky behavior for contracting cervical cancer was conducted by the anamnestic study "case-control". The study included 525 patients, among them 90 had abnormal PAP test (ASC-US, L-SIL, H-SIL and AIS). All of 90 patients underwent colposcopy. In five patients colposcopic findings were satisfactory and biopsy was not performed. In 85 participants with unsatisfactory findings, biopsy was performed. In 54 patients which form a study group, premalignant changes in the cervix uteri are

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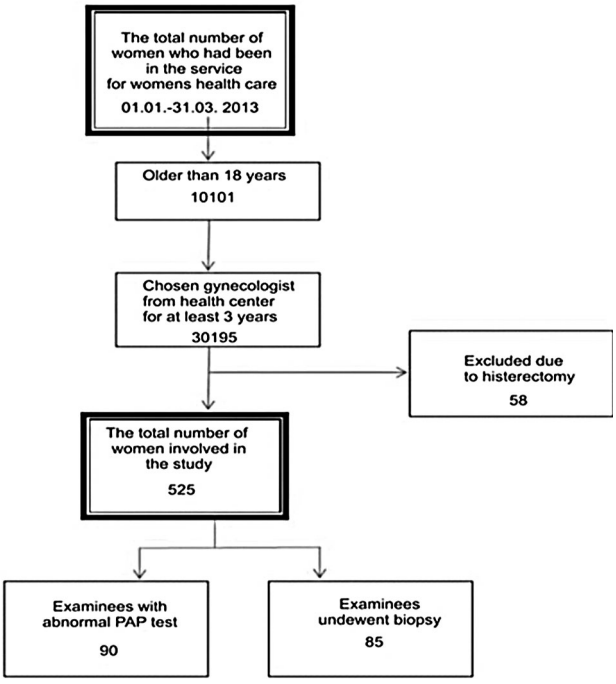
Figure 1. — Scheme of samples and the test population.



found (L-SIL, H-SIL, CIS), while the control group is represented by 31 respondents with benign changes in the cervix uteri (Figure 1).

All participants received a written notice in the form of informed consent and confirmed agreement. The data were obtained using a specially designed and pre-tested questionnaire, as well as by examining the medical records of patients. The questionnaire consisted of three groups of variables: socio-demographic variables, variables related to the behavior that are associated with risk for developing cervical cancer, and variables related to the application of diagnostic methods for cervical cancer. The socio-demographic characteristics that were investigated were: age, type of settlement (urban / rural), marital status (married / free, divorced, widowed), level of education (primary or secondary / high), self-assessment of financial status (very bad, bad / good, excellent). Behavior related variables were: smoking (more than 100 cigarettes during lifetime), the number of births (0, 1, 2, 3, and more), the number of abortions (0, 1, 2, 3, and more), the first sexual intercourse (< 18 / ≥ 18), the total number of sexual partners in a lifetime (> 4 / ≥ 4), the consistent application of condoms (yes / no), and personal history of sexually transmitted disease (yes / no). A part of the questionnaire related to the application of diagnostic methods for cervical cancer, were variables related to the interval of Pap test, and self-assessment of personal attitude towards Pap smears (acceptable / unacceptable). Biopsy results were obtained from medical records (benign / L-SIL, H-SIL, CIS).

Statistical analysis included descriptive statistics and statistical modeling methods. Descriptive statistical methods were used to analyze the distribution of the factors that are associated with cervical cancer (socio-demographic factors relating to the behavior, associated with risk of cervical cancer). Distributions frequency of selected variables are shown in comparison to HP biopsy (benign / L-SIL, H-SIL, CIS) and significance of the differences was tested by chi-square test. For a minimum level of statistical significance p <0.05 was used, while p <0.01 was taken as statistically high significance.Variables that showed high significance after univariate logistic regression were further tested by multivariate analysis, and association was expressed through odds ratio and 95% confidence interval. Logistic regression model was constructed to examine the association between each risk factor with an abnormal Pap test. Multivariate logistic regression obtained high significance for the following variables: early onset of sexual activity, more than four sexual partners, smoking, STD in personal history, and negative attitudes about Pap smear. Risk factors found to be significantly associated were included in the final model of logistic regression. The weight for factor was calculated based on regression coefficient (Reiter). Weights were assigned to risk factors and calculated for each respondent. Weighting coefficient for each of the above factors were applied to construct the risk index for cervical cancer. The final risk index was obtained by adding the weighted risk factors for each subject separately. Sensitivity and specificity for each of the statistically significant factors were calculated and receiver operating curve was constructed and used to identify cut-off point. For patients with pathological finding, Mann-Whitney test was applied by which high statistical significance (p <0.001) was confirmed. The analyzes were performed using SPSS software package (version 16).

Table 1. — *Histopathology.*

Histopathology		p
Benign	31 (36.5)	<0.000**
L-SIL [a]	30 (35.3)	
H-SIL [a]	18 (21.2)	
CIS [b]	6 (7.0)	
Total	85 (100.0)	

*[a]SIL - squamous intraepithelial lesion; [b]CIS - carcinoma in situ; **p < 0.01.*

Results

From total of 85 patients who underwent biopsy, on the basis of HP analyses, the authors found that 36.5% had no pathological changes of the cervix uteri, 35.3% of patients had L-SIL, 21.2% had H-SIL, and 7% had CIS. Distribution of women compared to HP findings are presented in Table 1

Pathological changes in the cervix uteri were more frequent in subjects that were not in a stabile relationships (75.7%), unlike those who had a steady partner (24.3%).

Table 2. — *Demographic and socio-economic characteristics of the respondents according to the histopathology.*

Characteristics	Benign (n, %)	SIL (n, %)	p
Age 40.13 (10.7)*			0.536
Partnership status			
Married/common law	22 (45.8)	26 (54.2)	0.041**
Single/divorced/widowed	9 (24.3)	28 (75.7)	
Education			
elementary	5 (50.0)	5 (50.0)	0.594
high school	18(33.3	36 (66.7)	
college / university	8 (38.1)	13 (61.9)	
Self-assessed socio-economic status			
unsatisfactory	7 (23.3)	23 (76.7)	0.063
satisfactory	24 (43.6)	31 (56.4)	

**mean (SD); **p < 0.0.*

Table 3. — *The frequencies of the variables related to behavior of the respondents and the histopathology findings.*

Characteristics	Benign (n, %)	SIL (n, %)	P
Ever smoking			
yes	19 (27.5)	50 (72.5)	<0.000**
never	12 (75.0)	4(25.0)	
Parity			
<3	25 (40.3)	37 (68.5)	0.226
≥3	6 (26.1)	17 (73.9)	
Abortion			
<3	21 (43.8)	27 (56.3)	0.129
≥3	8 (26.7)	22 (73.3)	
Age of first sexual intercourse			
<18	9(16.7)	45(83.3)	<0.000**
≥18	22 (73.3)	8 (26.7)	
Number of partners			
<4	20(50.0)	20(50.0)	0.022**
≥4	11(25.6)	32(74.4)	
Consistent use of condoms			
yes	2 (100.0)	0 (0.0)	0.047**
no	23 (32.4)	48 (67.6)	
History of STD***			
yes	6 (18.2)	27 (81.8)	0.006**
no	24 (46.6)	27 (53.4)	

***p < 0.01; ***STD - sexually transmitted diseases.*

Demographic and socioeconomic characteristics of respondents are presented in Table 2.

Variables related to the behavior, such as early sexual activity (23.6% were sexually active before the age of 18), inconsistency in the use of condoms (80.0% of respondents), history of STDs (13.0%), and smoking (53.9%) showed high statistical significance. The frequencies of the variables related to behavior of the respondents and the histopathology findings are presented in Table 3.

Examining a patient attitude towards controlling PAP swab and PAP testing frequency (interval between the individual controls) showed high statistical difference. The frequencies of the determinants related to use of preventive practices of the respondents according to the histopathology findings are presented in Table 4. The results for multivariate regression analysis for HP finding are presented in Table 5. There was a statistically significant difference for the following variables: early onset of sexual activity, smoking, STDs, personal history, and the negative attitude in taking the Pap smear.

In Table 6 the authors present factors that showed high statistical significance, making the risk model for development of malignancy on cervix uteri: the early onset of sexual activity, STDs in the personal history, and the negative attitude in taking the Pap smear. Figure 2 shows the ROC curve. Discrimination indicator, the AOC was 0.855, 95% CI (0.77-0.94).

Discussion

This study was designed to identify the risk factors for malignant changes of the cervix, to design a composite index to estimate the risk of cervical cancer, and to validate this index. This survey was conducted by the type of case-control study. HP findings obtained by biopsy of the cervix were used to assess the risk of premalignant changes in the cervix uteri. A number of factors significantly increase the

Table 4. — *The frequencies of the determinants related to use of preventive practices of the respondents according to the histopathology findings.*

Characteristics	Benign	SIL	P
Undertaking pap test			0.017**
once a year	19 (61.3)	16 (30.2)	
rarely	12 (38.7)	38 (69.8)	
Position on Pap smear			0.012**
unacceptable	5 (17.9)	23 (82.1)	
acceptable	26 (45.6)	31 (54.4)	

***p<0.01*

Table 5. — *Multivariate analysis according to the histopathology.*

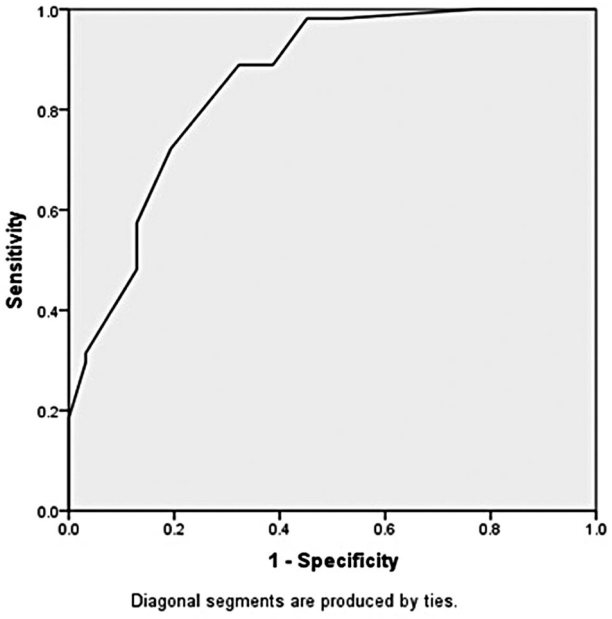
Characteristics	Multivariate analysis	
	Histopathology	
	OR (95%CI) *	P value
Partnership status		.
living alone	1.00	
married/common law	0.62 (0.14-2. 85)	0.541
Ever smoking		
yes	1.00	
never	**0.12 (0.01-1.01)**	**0.051**
History of STD		
yes	1.00	
no	**0.12 (0.02-0.78)**	**0.026****
Age of first sexual intercourse		
<18	1.00	
≥18	**0.03 (0.06-0.19)**	**<0.000****
Number of partners		
<4	1.00	
≥4	0.67 (0.1-4.48)	0.676
Undertaking pap test		
once a year	1.00	
for one or two years	5.57 (0.61-33.97)	0.138
rarely	0.56 (0.04-7.53)	0.661
Position on Pap smear		
unacceptable	1.00	
acceptable	**0.09 (0.00-0.87)**	**0.043****

**OR (95%CI); **p<0.01*

Table 6. — *Multivariate analysis.*

Characteristics	Multivariate analysis	
	Benign/SIL	
	OR (95%CI)	P value
Ever smoking		
yes	3.34 (0.68-16.48)	0.139
never	1.00	
History of STD		
yes	**0.12 (0.01-1.01)**	**0.051**
no	1.00	
Age of first sexual intercourse		
<18	**23.89 (4.92-115.95)**	**<0.000**
≥18	1.00	
Position onPap smear		
unacceptable	**7.82 (1.65-37.01)**	
acceptable	1.00	**0.009**

Figure 2. — ROC curve.



risk for cervical cancer, but aside from studies evaluating the individual risk factors, only a few studies have investigated and calculated the composite index of risk for cervical cancer [8, 9]. The composite index that consists of only three risk factors for cervical cancer was designed: early onset of sexual activity, STDs in the personal history, and the negative attitude of the Pap smear. Taking into account these three factors, it is possible to predict the malignant changes in validated sample with an overall accuracy of 0.855. The results obtained in this study were compared with the results of studies that determined the risk index for

the occurrence of cervical cancer [8, 9]. Depending on the specifics of the study population, study design and targeted populations, the authors have identified various factors that make up the risk index for cervical cancer.

There is a significant correlation between the development of cervical cancer and women's age. In the greatest risk of developing cervical cancer are women from 40-49 years old [11].

The impact of the level of education has been proven in studies of Indarty *et al.* and Patil *et al.* [8, 9]. Of all sociodemographic and reproductive determinants, in countries with a low standard of living, education is an essential cofactor for cervical cancer. [11]

Wilkinson *et al.* allocated the period of smoking history as a significant risk factor for the occurrence of cervical cancer [12] and the risk of this malignancy significantly increases with intensity and length of the smoking history [13].

Early sexual activity (before 18 years of age) showed a highly statistical significance in the occurrence of abnormal HP findings and entered as a significant risk factor in the model index. Age at the onset of sexual activity is a significant risk factor for developing cervical cancer [14]. Indarty *et al.* and Wilkinson *et al.* [8, 12] pointed out that the greater number of sexual partners is a dominant risk factor in creating model of risk index. In the study of Reiter *et al.* [15], a history of STDs was highly statistically significant risk factor for abnormal Pap test and entered the model of risk for cervical cancer. Although there is clinical evidence that HPV is the main etiological factor for cervical cancer, other sexually transmitted diseases can also affect the occurrence of this malignancy.

Studies of Indarty *et al.* and Wilkinson *et al.* have allocated beneficiaries of oral contraceptives as a high risk of developing cervical cancer [8, 12] The interval of application represents the most significant risk factor for developing cervical cancer [16]. Women with high parity (more than three births) are at risk for developing cervical cancer. The study of Patyl *et al.* allocated multiparity as a risk factor that enters into the composition of risk index model [9].

Numerous studies have shown that failure to respond to the screening, or the screening interval longer than five years, represented a significant risk factor which results in diagnosis of invasive cervical cancer [17, 18].

Unlike other studies that have determined the risk index for cervical cancer [9], this study, as well as some studies of Indarty *et al.*, included factors related to the methods used for early detection of cervical cancer, as we know that non-application of preventive screening practices, as well as non-implementation of screening, are the significant factors in making the diagnosis of an advanced stage of the disease [8].

In this study, the attitude of the examinees to subject to the PAP smears testing, proved to be an important risk factor. Respondents who had a negative attitude constituted a risk group. The negative experiences of patients in primary care, and the lack of knowledge of women about cervical cancer also influence the application of preventive measures. The present authors found no data in the literature regarding the application of the risk index of cervical cancer, except in the study of Quinn *et al.* [19], who reported on the index developed by Wilkinson *et al.* [12].

Conclusion

This study identified three risk factors (early sexual activity, STDs, and non-implementation of the screening) for creating a model of risk index for cervical cancer. The application of this index would be helpful for doctors in primary healthcare (gynecologists and family medicine physicians) for identifying women who are at increased risk for developing cervical cancer and is important in future research, educational programs, and recommendations for additional screening.

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Corresponding Author:
L. TASIC. M.D.
University of Belgrade, Faculty of Medicine
Gynecology Obstetric Clinic "Narodni Front"
Pere Velimirovica 12 A
Belgrade (Serbia)
e-mail: lisatasic1234@gmail.com