

## IMPACT OF SOCIO-DEMOGRAPHIC FACTORS ON THE DELAYED DIAGNOSIS AND ADVANCED STAGE PRESENTATION OF PATIENTS WITH INVASIVE CERVICAL CANCER IN MACEDONIA

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### Abstract

*Aim:* The study aims to establish certain socio-demographic factors associated with delayed presentation (i.e. advanced stage at diagnosis) in patients with invasive cervical cancer in Macedonia.

*Materials and methods:* The cross-sectional study was conducted with patients already diagnosed and treated for invasive cancer of the uterine cervix who came in for their regular annual check-up at the University Radiotherapy and Oncology Clinic, Medical Faculty, Ss. Cyril and Methodius University in Skopje, Macedonia. The data were collected by interviewing the participants using a standardized questionnaire.

*Results:* A total of 115 patients were recruited in the study. Eight of them were excluded from further analysis due to incomplete data. Close to 72% of the patients analysed presented with advanced stage disease, while 28.04% of the patients were diagnosed with early stage disease. The univariate analysis and Chi-square statistics showed that the patients had a higher probability of being diagnosed with advanced stage disease if they had a low monthly income ( $p = 0.01$ ), had lower degrees of education ( $p < 0.001$ ), had an unsatisfactory level of genital hygiene ( $p < 0.001$ ) and had no family history of invasive cervical cancer in first degree female relatives ( $p = 0.003$ ).

*Discussion:* The results from the study could be utilized to identify the population at risk which should be targeted for implementation of specialized educational programmes for familiarizing the population with the nature of the disease which in turn would increase the level of consciousness as a step towards implementing a national screening programme.

**Key words:** cervical cancer, socio-demographic factors, stage at diagnosis, delayed diagnosis.

### Introduction

Invasive cancer of the uterine cervix is the second most common malignancy in females in the world [1]. The incidence is estimated at around 529,000 cases annually which corresponds with a worldwide age-standardized incidence rate (ASR) of 15.2 per 100,000 [2]. In 2008 there were 274,883 lethal outcomes associated with the disease worldwide, which account for 8% of the total global morbidity associated

with malignant neoplasms in the female population [2]. Still, the developed countries mark a continuous decline in the incidence and mortality rates from the 50s onward. This decline is attributed to the wide implementation of screening programmes utilizing exfoliative cytology (conventional smear or liquid-based cytology – LBC) which facilitates the detection of early precursor lesions [3]. Apart from the screening programmes, the improvements of the surgical and

radiological techniques for treatment have increased the survival rates even further in patients with malignant neoplasms of the uterine cervix.

Macedonia has a high incidence of cervical cancer. Approximately 200 new cases are registered each year, which makes cervical cancer the second most common neoplasm in females in the country. According to the GLOBOCAN data for 2008, Macedonia has an ASR of 22.0 per 100,000 women annually, which is more than twice the average European ASR (10 per 100,000 women).

In spite of the fact that the national health policies in Macedonia state the decrease of morbidity and mortality associated with cervical cancer as one of the top priorities, currently there is no organized national cytological screening programme. That in turn implies the need for implementation of alternative strategies for prevention and disease control including opportunistic screening and education of the mass population about the risk factors that contribute to the development of the disease and the use of barrier contraceptive methods [4].

Invasive cancer of the uterine cervix remains a disease which is closely linked to the socio-economic and demographic disparities in the developed as well as the developing countries. Despite the global downward trend of the incidence of cervical cancer in the US, there are still certain disparities in the mortality rates associated with different age, ethnic and socio-demographic population groups. Nelson et al. [5] and Couglin et al. [6] published that race, ethnicity, age over 65, a lower degree of education and life in rural parts of the country were associated with inadequate screening in the investigated population. The analysis of the data of the cancer registries in USA showed that the cervical cancer mortality rates increase proportionally with the degree of poverty and lower degrees of education. In addition, a negative correlation between the socio-economic groups and the stage of the disease at diagnosis has been well established [7]. Late stage diagnosis is correlated with lower rates of survival in these patients [8].

### **Aim**

The study aims to establish certain socio-demographic factors associated with delayed presentation (i.e. advanced stage at diagnosis) in patients with invasive cervical cancer in Macedonia.

## **Materials and methods**

### *Study design*

The cross-sectional study was conducted with patients already diagnosed and treated for invasive cancer of the uterine cervix who came in for their regular annual check-up at the University Radiotherapy and Oncology Clinic, Medical Faculty, Ss. Cyril and Methodius University in Skopje, Macedonia. The patients were recruited by random choice from September to December 2012. The data was collected by interviewing the participants using a standardized questionnaire. Before the interview, all patients received detailed oral and written information about the study and informed consent for participation in the study was acquired. The questionnaire contained the following information: age (categorized in three age groups: 0–24, 25–39 and over 50 years), nationality, degree of education (no education, elementary education, high school, college and/or higher degree), monthly income (categorized as low i.e. < 20,000 MKD, average 20,000–40,000 MKD and above average > 40,000 MKD), marital status, place of residence (urban vs. rural), disease stage at diagnosis (categorized as early – FIGO Stage I and II and advanced – FIGO Stage III and IV), number of lifetime sexual partners, number of pregnancies, parity, degree of genital hygiene (satisfactory i.e. the patients douches at least once daily vs. unsatisfactory if the patient douches less often), family history of the disease (first-degree relative diagnosed with invasive cervical cancer) and presence of other infectious agents besides human papillomavirus (HPV).

### *Statistical analysis*

Upon acquisition, the data were entered in a computerized database and compared with regard to the disease stage at diagnosis and the socio-demographic factors in question. Chi-square test was used to test the statistical association between the socio-demographic factors and the stage of the disease at the time of presentation. The odds ratios (OR) and their 95% confidence intervals (CI) for the different socio-demographic factors were calculated using a logistic regression model. OR were modelled using the linear relationship between the socio-demographic factors and the logit of the probability of disease. All statistical calculations were done using IBM SPSS Statistics for Windows version 20.0.

## Results

A total of 115 patients were recruited in the study. Eight of them were excluded from further analysis due to incomplete data. The average age was  $50.7 \pm 12$  (range, 27–76) years. The ethnicity of the patients was as follows: 85.05% were Macedonian, 5.61% were Albanian and 9.34% were of one of the minor ethnic groups represented in Macedonia. A similar distribution was detected in regard to religious beliefs: 84.11% of the patients declared themselves as Orthodox Christians, while 15.89% were Muslims. With regard to the place of residence, 61.68% of the patients lived in urban communities, while 38.32% lived in rural com-

munities. Slightly over 40% of the patients were illiterate or had not completed elementary education, 28.04% of the patients had elementary education, 19.63% had completed high school and the remaining 12.15% had higher degrees of education. Approximately 74% of the patients classified their monthly income as below average, 16% had an average monthly income and close to 10% had above average monthly income. Most of the patients recruited in the study were married (82.24%), 3.74% were single and 14.02% were widowed.

Table 1 shows the different socio-demographic and socio-economic factors analysed and their association with the disease stage at

Table 1

*Distribution of socio-economic and demographic risk factors according to disease stage*

Factor	Stage of the disease		P-value
	Early	Advanced	
<b>Age (years)</b>			0.065
0–24	9	11	
25–49	14	34	
≥ 50	7	32	
<b>Nationality</b>			0.066
Macedonian	27	64	
Albanian	3	3	
Other	0	10	
<b>Religion</b>			0.46
Orthodox Christian	27	63	
Muslim	3	14	
<b>Education</b>			< 0.001*
No education	9	34	
Elementary education	4	26	
High school	8	13	
College or higher education	9	4	
<b>Average monthly income</b>			0.01*
< 20000 MKD	17	62	
20000–40000 MKD	6	11	
> 40000 MKD	7	4	
<b>Marital status</b>			0.742
Single	1	3	
Married	26	62	
Widowed	3	12	
<b>Place of residence</b>			0.823
Urban community	18	48	
Rural community	12	29	
<b>Level of genital hygiene</b>			< 0.001*
Unsatisfactory	6	50	
Satisfactory	24	27	

<b>Family case-histories</b>			0.003*
Negative	13	57	
Positive	17	20	
<b>Infections (excluding HPV)</b>			0.583
Denies	6	12	
Other agent present	24	65	

\*Statistically significant difference at 10% level

diagnosis. Close to 72% of the analysed patients presented with advanced stage disease, while 28.04% of the patients were diagnosed with early stage disease. The univariate analysis and Chi-square statistics showed that the patients had a higher probability of being diagnosed with advanced stage disease if they had a low monthly income ( $p = 0.01$ ), had lower degrees of education ( $p < 0.001$ ), had an unsatisfactory level of genital hygiene ( $p < 0.001$ ) and had no family history of invasive cervical cancer in first degree female relatives ( $p = 0.003$ ).

Table 2 shows the distribution of patients according to disease stage with regard to number of pregnancies, parity and number of lifetime sexual partners. 76% of the patients belong-

ing to the group with early stage disease had had fewer than 3 pregnancies, while 45.46% of the patients with advanced stage disease had had 4 or more pregnancies. The difference was not statistically significant ( $p = 0.0614$ ). In spite of the fact that the patients belonging to the advanced stage group had a higher number of pregnancies, both groups had an almost equal number of children (83.33% and 84.42% of the patients in the two groups had 3 or fewer children, respectively). With regard to the number of lifetime sexual partners, the vast majority of the patients belonging to both groups declared having 2 or fewer lifetime sexual partners (80% and 75.32%, respectively).

Table 2

*Distribution of patients' number of pregnancies, parity and number of lifetime sexual partners according to disease stage*

Factor	Stage of the disease		P-value
	Early	Advanced	
<b>Number of pregnancies</b>			0.316
0	1	2	
1	2	5	
2	10	16	
3	10	19	
≥ 4	7	35	
<b>Parity</b>			0.133
0	1	2	
1	5	10	
2	19	31	
3	2	22	
≥ 4	5	12	
<b>Number of lifetime sexual partners</b>			0.115
1	17	49	
2	7	9	
3	4	5	
≥ 4	2	16	

The results of the multivariate binary logistic regression with regard to the disease stage at the time of diagnosis are presented in Table

3. According to the results it is evident that the patients in this study had a higher probability of being diagnosed with advanced stage disease

if they had a lower degree of education (no education and elementary education OR = 9 and OR = 7.54, respectively), a lower average monthly income (OR = 13.17 and OR = 10.55 for below average and average monthly income, respectively), unsatisfactory genital hygiene (OR = 5.37) and no family history of invasive cervical cancer (OR = 6.42).

Table 3

*Multivariate binary logistic regression for identified significant risk factors for advanced stage presentation*

Factor	OR	95% CI	
		Lower	Upper
<b>Degree of education</b>			
No education	9.001	1.619	50.035
Elementary education	7.446	1.109	50.000
High school	6.339	0.924	43.482
<b>Average monthly income</b>			
< 20000 MKD	13.165	2.042	84.894
20000–40000 MKD	10.551	1.278	87.110
<b>Level of genital hygiene</b>			
Unsatisfactory	5.369	1.490	19.356
<b>Family history</b>			
No history	6.415	1.885	21.839

### Discussion

In our study we investigated the impact of different socio-economic and demographic factors on advanced stage presentation in a population of patients diagnosed with invasive cancer of the uterine cervix. Patients had a higher probability of being diagnosed with advanced stage disease if they had a lower degree of education, a lower average monthly income, unsatisfactory genital hygiene and no family history of invasive cervical cancer.

In our series 71.96% of the patients interviewed had been diagnosed with advanced stage disease. It is clear that the disease stage at the time of presentation is the single most important independent prognostic factor influencing the mortality rate [9, 10]. The five-year survival rate decreases proportionally to disease stage from over 85% for stage IB to 0–20% for stage IVA [11, 12]. Likewise, the risk of pelvic disease recurrence increases proportionally with advanced stage from 10% for a patient with stage IB disease to over 75% for patients with stage IVA disease [2]. Finally, the risk of distant metastases follows the same pattern, i.e. it increases with advanced stage from 16% for stage I, 25% for stage II, 39% for stage III and 75% for stage IV disease [13].

Even though the available literature has very limited data on the impact of socio-economic

and demographic factors on the delayed presentation of invasive cervical cancer, one should note their influence on patient compliance with established screening programmes. The results from our study are in concordance with the observations from the studies conducted in the USA which concluded that patients with lower socio-economic status had a lesser probability of active participation in the programmes for disease prevention and screening [5, 6].

The degree of education is clearly linked to the average income and the degree of understanding and receiving of health education [14, 15], which in turn means that the increased risk of advanced stage presentation of invasive cervical cancer in women with a lower degree of education may be connected with insufficient knowledge of the nature of the disease and the possibilities of its prevention. Two studies conducted in patients with invasive cervical cancer in New York (n = 2930) and Florida (n = 852) failed to establish an association between advanced stage disease and the degree of education after adjusting for differences in the average annual income and marital status [16, 17]. Nevertheless, the Florida study [16] as well as another American study conducted in five states and five urban areas found that women with lower degrees of education had a higher probability of having more extensive loco-regional

cancer spread when compared with women with higher degrees of education (37% vs. 51% and 31% vs. 38%, respectively). The statistical analysis in all three studies acquired the data for the degree of education from the average degree of education for the given geographical region (i.e. average degree of education and/or proportion of patients with high school education), thus having a lower approximation of the relative risk for the outcomes when compared to individualized socio-economic indicators [18]. Our study included individualized data, which we think makes them adequate and valid for the evaluation of the individual effect of the degree of education on late stage presentation.

In our study an association between the average monthly income and the advanced stage presentation of the disease was identified. A similar study conducted in Denmark failed to identify such a risk after adjusting for the degree of education and the marital status [19]. The data from the American studies are also conflicting. In one study conducted in four large urban areas in USA ( $n = 32305$ ), the patients living in areas with a low or average monthly income had a higher probability of having advanced-stage disease at the time of presentation (OR = 1.43 and 1.25;  $p = 0.01$ ) when compared with women who lived in areas with a higher monthly income [20]. Ferrante et al. [16] and Mandelbatt et al. [17] found an association between advanced-stage disease and the average income, while McCarthy et al. [21], Barry et al. [22] and Singh et al. [8] report that patients living in areas where 60%, 40% and 20% of the general population was impoverished had a 20%, 50% and 20% higher risk of advanced stage presentation, respectively. Yet none of these studies included individualized data for the average income of the patients and made an adjustment for the degree of education.

Most of the published studies fail to find an association between the level of genital hygiene and cervical cancer [23, 24]. However, studies conducted in entirely rural populations in developing countries in Africa [25, 26] and China [27] demonstrate a significant increase of risk due to poor genital hygiene. In the two studies conducted in Africa, the association remains even after adjusting for HPV infection. Our study identified poor genital hygiene as a risk factor for advanced stage presentation of

cervical cancer. This is probably due to the low level of consciousness of the patients regarding their own genital health.

It is relatively clear that there is a certain genetic predisposition for the development of invasive cancer of the uterine cervix, which is related to the mutation of the genes controlling the immune response towards HPV infection and the replication of viral DNA [28, 29]. According to our research, having no family history of the disease is associated with a higher risk of advanced stage of the disease at diagnosis. These conflicting results might be partly due to the fact that patients with no family history of the disease had no first-hand experience of the disease, and partly due to the reporting bias.

Our study certainly had some limitations. First of all it is a retrospective analysis and most of the data was collected by interviewing the patients, which gives rise to the possibility of reporting bias. For example, the HPV status of the patients diagnosed more than three years ago could not be verified because the database in our institution had data for the patients diagnosed in the last three years only, so we had to rely on the data acquired from the interview. Some (if not most) of the patients might have given false information with regard to the number of lifetime sexual partners due to social and/or religious norms. Part of the data was acquired from medical histories, a large part of which is hand written from medical personnel who did not put too much of an effort into the accuracy of the records. Second, the sample size is small. The patients were recruited by random choice and the sample does not reflect the real distribution of the different groups in the general population (i.e. most of the patients were Macedonian, predominantly in advanced stages of the disease. We also did not include a sufficient number of patients detected in early stages who were treated by surgery only – a group of patients which is expected to be younger, with higher degrees of education and/or higher degrees of average income).

Nevertheless, the study correctly identified certain of the risk factors for delayed presentation and advanced stage diagnosis of invasive cancer of the uterine cervix. The results from the study could be utilized to identify the population at risk which should be targeted for

implementation of specialized educational programmes for familiarizing the population with the nature of the disease which in turn would increase the level of consciousness as a step towards implementing a national screening programme. The study could also serve as a guide for future larger studies conducted on larger and more adequate samples that would yield more relevant data which would be representative of the general population in Macedonia, so that one could target the high-risk groups in order to diagnose the disease in an early stage when the patients have a higher chance of prevention, cure and/or better disease-free survival.

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## Резиме

### **ВЛИЈАНИЕ НА СОЦИО-ДЕМОГРАФСКИТЕ ФАКТОРИ НА ОДЛОЖЕНОТО ДИЈАГНОСТИЦИРАЊЕ И НАПРЕДНИОТ СТАДИУМ НА БОЛЕСТА ВО МОМЕНТ НА ПРЕЗЕНТИРАЊЕ КАЈ ПАЦИЕНТИТЕ СО ИНВАЗИВЕН ЦЕРВИКАЛЕН КАРЦИНОМ ВО РЕПУБЛИКА МАКЕДОНИЈА**

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*Цел:* Студијата има за цел да ги одреди социо-демографските фактори кои се асоцирани со одложеното дијагностицирање (т.е. напредниот стадиум на болеста во моментот на дија-

гноза) на пациентите со инвазивен цервикален карцином во Македонија.

*Материјал и методи:* Оваа пресечна студија е спроведена кај пациентки кои веќе се дијагностицирани и третирани за инвазивен цервикален карцином, кои се јавиле за редовна годишна контрола на Универзитетската клиника за радиотерапија и онкологија, Медицински факултет, Универзитет „Св. Кирил и Методиј“ во Скопје, Македонија. Податоците беа собирани преку интервјуирање на учесниците со стандардизиран прашалник.

*Резултати:* Во студијата беа вклучени вкупно 115 пациентки. Осум од нив беа исклучени од понатамошната статистичка анализа поради некомплетни податоци. Речиси 72% од пациентките беа презентирани во напреднат стадиум на болеста, а 28,04% од пациентките беа дијагностицирани во ран стадиум на болеста. Униваријатната анализа и Хи-квадрат статистиката покажаа дека пациентките имале поголема веројатност да бидат дијагностицирани со напреднат стадиум на болеста доколку имаат ниски месечни примања ( $p = 0,01$ ), потоа ниско ниво на образование ( $p < 0,001$ ), незадоволителен степен на генитална хигиена ( $p < 0,001$ ) и немаат фамилијарна анамнеза за инвазивен цервикален карцином кај женските роднини од прво колена ( $p = 0,003$ ).

*Дискусија:* Резултатите од студијата можат да бидат искористени за да се идентификува ризичната популација која треба да биде цел на имплементацијата на специјализираните образовни програми за запознавање на популацијата со природата на болеста, а со тоа ќе се зголеми нивото на свеста за болеста, како меѓучекор до имплементација на националната скрининг програма за цервикален карцином.

**Клучни зборови:** цервикален карцином, социо-демографски фактори, стадиум во момент на дијагноза, одложено дијагностицирање.