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Risk Factors in a Sample of Patients with Advanced Cervical Cancer

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Abstract
The estimated burden of neoplasia of uterine cervix in the 27 EU member states sums up to 34300 cases and 16200 death, with higher incidence and mortality in eastern countries. A number of risk factors increase the likelihood of developing cervical cancer. Even if the risk factors significantly increase the chances of developing cervical cancer, a large number of women with risk factors do not develop the disease, and when a woman develops cancer or precancerous lesions in the cervix may be difficult to establish the causal relationship with certain risk factors. The present study aimed to appreciate the presence and magnitude of risk factors for patients diagnosed with advanced cervical cancer and to outline best strategies to reduce the incidence of this neoplasia, and improve prognosis. Risk factors have been investigated in 42 patients diagnosed with advanced cervical cancer using HPV genotyped determination and a questionnaire for the evaluation of cervical cancer risk factors. In our sample of patients a high risk profile is shaping for low socio-economical level, modulated by the impact of HPV infection with high risk stains of virus, overweight-obesity, smoking and inadequate cervical cancer screening. In this frame a special alarm signal is represented by the very high percentage of patients with overweight and obesity. From the public health perspective, we consider that efforts should be focused on preventing weight gain, regular screening and health education field.

Keywords: Risk; Cervical cancer; HPV (Human Papilloma Virus); Obesity; Pap smear.

Introduction

According to World Health Organization (WHO), 58.8 million people died in 2004 [1], and cancer accounted for around one in eight of all deaths. Accounting for an estimated 493000

incident cases, 1.4 million prevalent cases and 273000 deaths in the world in 2002, being responsible for approximately 8% of the global burden of cancer among women, and the second most common cancer among women worldwide, cervical cancer emerge as an important global public health problem.

However, it is noted a more than twenty fold difference between the highest and lowest incidence rates of cervical cancer worldwide [2, 3]. Regional variations in incidence of cervical cancer were the basis for public health concerns in the area, but were also the source of formulating hypotheses about the risk factors involved in the etiology of this cancer, factors that could be responsible for these differences.

In Europe, the map of cervical cancer mortality in women older than 45 years shows particularly high figures in Eastern Europe, but this neoplasia is still a significant public health problem for entire Europe. Dramatic contrast between western and eastern states deserves particular attention from the countries concerned, but also by EU. Romania, with a population of 9.44 millions of women aged 15 years and older at risk of developing cervical cancer ranks at the top of member states with highest cervical incidence and cancer death rates. In Romania, cervical cancer is the 3rd most frequent cancer among women, and the most frequent among women between 15 and 44 years old.

In total, the estimated burden of neoplasia of uterine cervix in the 27 EU member states sums up to 34 300 cases and 16 200 death [4]. The addition of Romania and Bulgaria made the west-east gradient even stronger than before the expansion of EU [5].

A number of risk factors increase the likelihood of developing cervical cancer. It was noted that women who have not risk factors, rarely develop this malignancy. Even if the risk factors significantly increase the chances of developing cervical cancer, a large number of women with risk factors do not develop the disease, and when a woman develops cancer or precancerous lesions in the cervix it may be difficult to establish the causal relationship with certain risk factors.

In addressing the risk factors from the public health perspective is essential to focus on those factors that can be avoided or modified (such as smoking, infection with Human Papilloma Virus, etc). However, is also important to know the non-modifiable risk factors (age, family history), because for women with these risk factors making regular screening tests is even more recommended for early detection of cervical neoplasia.

Purpose

The present study aimed to appreciate the presence and magnitude of risk factors for cervical cancer in patients diagnosed with advanced neoplasia of cervix, and to outline the best strategies to reduce the incidence of this neoplasia and to improve the prognosis.

Material and Method

Patients were enrolled in this prospective study from "Ion Chiricuta" - Cancer Institute, Cluj-Napoca, Romania. Approval for this study was obtained from the Institutional Ethics Committee, and all study subjects were provided written informed consent.

Risk factors have been investigated in 42 patients diagnosed with advanced cervical cancer using HPV genotyping testing method and a questionnaire for the evaluation of cervical cancer risk factors. The HPV genotyping was based on the LINEAR ARRAY HPV (Human Papilloma Virus) genotyping Test. The test utilizes amplification of target DNA by the polymerase Chain Reaction (PCR) and nucleic acid hybridization and detects thirty seven anogenital HPV DNA genotypes (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45,, 68, 69, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73 (MM9), 81, 82 (MM4), 83 (MM7), 84 (MM8), IS39 and CP108, collected in PreservCyt® Solution. From every sample were used 2 ml of collected solution containing the cervical cells. The DNA amplification was made on LightCycler 480 instrument (Roche Technologies) based on a specific program: 9 min at 95°C followed by 40 cycles of 30 s at 95°C and 1 min at 55°C and 1 min at 72°C for the amplification step, finalized on a cycle of 5 min at 72°C.

The HPV genotypes were evaluated with Linear Array HPV strip by a hybridization procedure. The results interpretation was made by placing the LINEAR ARRAY HPV Genotyping Test Reference Guide over the strip in the cut out area so that the HPV genotype reference lines appear on each side of the strip.

The genotype classification according with risk used in this study is presented in Table 1.

Table 1. HPV genotype classification according with risk

Classification	Strain
High risk HPV genotype	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
HPV genotype with **probability of high risk**	26, 53, 66, 68, 73, 82
Medium risk HPV genotype	42, 55, 61, 62, 64, 67, 69, 71, 72, 81, 83 (MM7), 84 (MM8), IS39, CP6 108
Low risk HPV genotype	6, 11,40, 54, 70

The questionnaire includes 68 core questions structured in 5 category modules: socio-demographic, health status, medical and reproductive history, lifestyle. The attention was focused on main risk factors. In this respect, the module of medical and reproductive history includes questions regarding age of becoming sexual active, number of sexual partners during lifetime, history of Pap smears testing, pre-cancer lesions on uteri cervix, the history of sexually transmitted diseases (gonorrhea, syphilis, herpes, Chlamydia, genital warts), number of pregnancies and childbirths, exogenous hormone use (contraceptives and hormone replacement therapy), family history of cervical cancer. The module of lifestyle includes questions referring smoking (including passive smoking), alcohol consumption, and dietary habits. The data were introduced in an Excel data base for analyzing. For quantitative data mean and standard deviation was used to present it, for qualitative data the percentages were used, along with 95% confidence intervals.

Body Mass Index has been used in order to assess adiposity. Recommended WHO BMI (Body Mass Index) cut-off points have been used [6,7].

Results

Several risk factors for the development of cervical cancer, including: Human Papillomavirus (HPV) infection, family history of cervical cancer, age, sexual and reproductive history, socioeconomic status, smoking, long-term use of oral contraceptives, obesity were assessed.

Human Papillomavirus (HPV) Infection

On 97.06% (CI 95%) patients from our sample, the HPV serology has been positive, with 85.30% (CI 95%) patients infected with HPV strains of high risk, and 11.76% (CI 95%) with HPV genotypes considered with probability of high risk (Figure 1). High risk strains identified were 16, 31, 33, 45, 51, 58, and medium risk strains 81 and 84.

Family History of Cervical Cancer

In our sample of patients, only 13.33% (CI 95%) have a positive familial history of cervical cancer (Figure 2).

Age

The mean age in our sample of patients was 49.96 (SD=11.74), the younger age 23, and the older 74. The youngest patient has a positive cervical cancer history in a first-degree relative (mother).

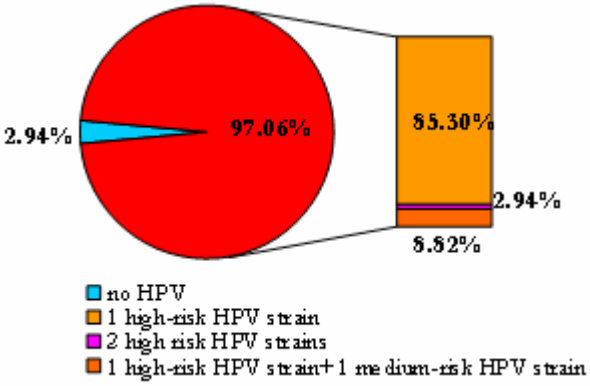

Figure 1. HPV serology

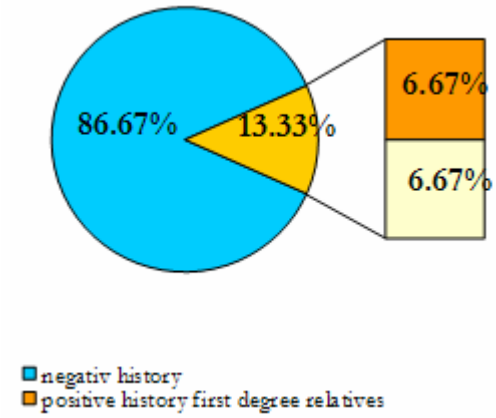

Figure 2. Sample distribution according with family history of cervical cancer

Sexual and Reproductive History

Epidemiological studies have shown an increased risk for invasive cervical cancer attributable to sexual and reproductive behavior.

The analyze of our data revealed that more than 4 in 10 interviewed patients have became sexually actives before the age of 18, and more than one third had more sexual partners during lifetime. Also it should be mentioned that the large majority of patients' life partners had affirmatively multiple partners during lifetime, which increases the risk of acquiring HPV infection. 37.48% patients had 3 or more childbirth (Table 2).

Table 2. Sample distribution according with sexual and reproductive indicators (%)

Category	Before age of 18	After age of 18	1 partner	> 1 partner	Do not know	0	1	2	≥3
First sexual intercourse	**41.67**	**58.33**							
Number of sexual partners, lifetime			**66.67**	**33.33**					
Partner's number of partners			**16.67**	**69.05**	**14.29**				
Number of childbirths						**13.4**	**4.35**	**47.84**	**37.48**

Socioeconomic Status

From our sample of patients 66.67% are residents in rural area. In Romania still persist marked rural-urban gaps in terms of socio-economic status. The inhabitants from rural areas face in a large proportion poverty and a more difficult access to health care services. Health problems of women

from rural area are often linked to nutritional deficiencies, excessive workload and higher number of pregnancies and births, along with a low level of education.

One third of interviewed patients declared having a poor economical condition and only 20% of them a good socio-economic status. Low socioeconomic status has proven to be a significant risk factor for invasive cervical cancer due to its large impact on education and medical resources for early detection of cervical cancer and treatment in early stages.

A lower risk was associated with higher level of education. In our sample, only 23.68% of patients have a high level of education (Table 3).

Table 3. Socio-demographic characteristics

Category	Urban %	Rural %	Low %	High %	Good %	Satisfactory %	Poor %	Married %	Single %
Residence	**33.33**	**66.67**							
Level of education			**76.32**	**23.68**					
Socio-economic status					**20.00**	**46.67**	**33.33**		
Marital status								**71.88**	**28.12**

The increased risk with low socioeconomic status is attributed mainly to the non attendance of screening, and by consequence failure of treating precancerous conditions, and also to the lack of knowledge about prevention of HPV infection.

Most of women with cervical cancer experience a long asymptomatic period before the clinical onset of disease. During this time, exfoliation of cervical cell is a continuous process and therefore early recognition of abnormal cytological changes through regular screening offers early detection and protection against progression from pre invasive to invasive stage of disease.

Our data document a very low rate of participation in cervical screening programs. A worrying 61.11% patients in our sample declared they have never been screened for cervical cancer, and from those ever screened, only 2.75% have been screened annually and 11.11% at 2 years interval (Figure 3).

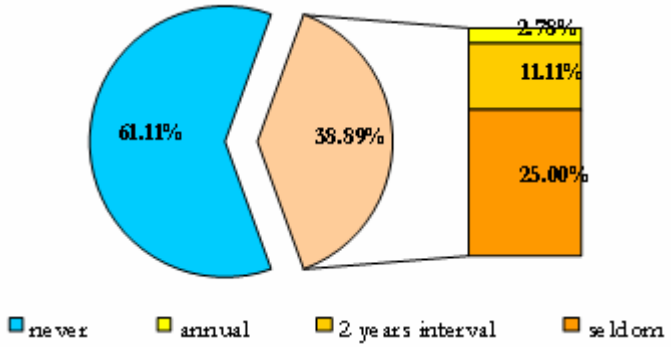

Figure 3. Sample distribution according with Pap smears frequency

Characteristics of patients that reported being screened annually or at two years interval were: younger ages, lean, residents in urban area, high level of education, and good socio-economical status.

Smoking

Smoking has been suspected for long time to be a risk factor for cervical cancer. Even if in our sample only 33.33% patients were active smokers, more than two thirds of them declared being exposed to other people tobacco smoke at home as adults, and almost 4 in 10 of them during childhood (Table 4).

Table 4. Tobacco smoke exposure

Category	Yes (%)	No (%)	Childhood		Adulthood	
			Yes (%)	No (%)	Yes (%)	No (%)
Active smokers	**33.33**	**66.67**				
Passive smokers			**36.67**	**63.33**	**66.67**	**33.33**

Oral contraceptives

31.43% patients in our sample only have used oral contraceptives, but no one of them for a longer than 5 years period of time.

Obesity

The analyze of our sample according with BMI values, using recommended WHO BMI cut-off points to classify normal weight, underweight, overweight and obesity in adults, revealed an alarming situation, almost three quarters (74.29%) of patients being overweight (34.29%) and obese (8.57% class I, 14.29% class II, and 17.14% class III) (Figure 4).

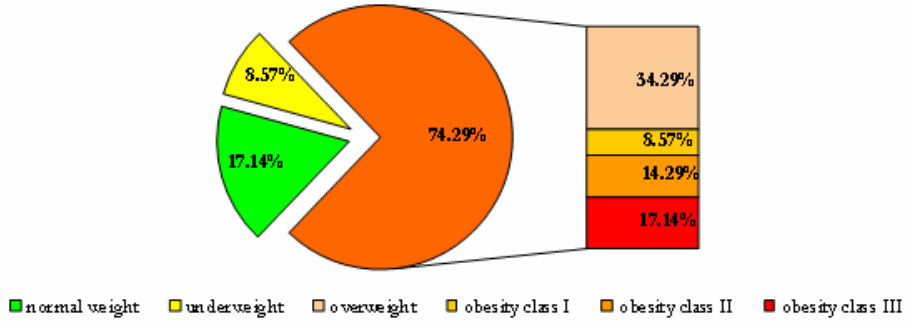

Figure 4. Sample distribution according with BMI value

Discussion

Our data showed that almost all enrolled patients were HPV positive with the large majority of them being infected with high-risk strains. During lifetime, many women are infected with HPV, but few will develop cervical cancer. In most cases the immune system fights the virus, leading to its removal without treatment. However, for reasons not yet understood, in some women the infection persists and can cause cervical cancer. HPV is among the most common sexually transmitted diseases and occurs in young women, being less common after 30 years. Within two years most women clear the infection without complications. Yet, long term infection with high-risk strains of HPV can lead to the development of cervical dysplasia and cancer [9]. The risk of dysplasia and cancer after the infection with HPV appear to be dependent on the amount of virus during infection and the duration of its persistence [11]. Data on the HPV burden in general population of Romania is not available, but in Eastern Europe, the region Romania belongs to, around 22.3% of women in general population are estimated as hosting a HPV infection at a given point during lifetime, and 74.5% of invasive cancer are attributed to HPVs 16 or 18 [12].

Although in our sample only few patients had positive history for cervical cancer it is well recognized the fact that cancer aggregated in families, first degree relatives of a cancer patient having an increased risk of same or different site cancers. For some cancers it was noticed a 2-3 fold increase in risk for those with a positive family history as against general population [13], but it is not yet clear if the risk associated with family history of cancer is due to a genetic susceptibility, or to shared environmental and lifestyle influences [14]. The youngest patient in our sample had a positive history of cervical cancer in a first degree relative (mother). It has been documented that women with a family history of cervical cancer, especially in first degree relatives, have a two-fold risk of developing cervical cancer, suggesting an inherited susceptibility [15].

The mean age in our sample was under 50 years. Most cases of cervical cancer are diagnosed in women younger than 50 and very few in women younger than 20. The risk decreases after age 55, but still 20% of cases occur in older women, the risk of cervical cancer not disappearing all together with age. According to American Cancer Society, this pattern seems to be the result of to two conflicting factors, changes in sexual behaviors and the tendency of genetic mutations to accumulate over time [16].

Our data showed that a large proportion of patients in our sample became sexually active at young ages and during lifetime had more than one sexual partner. Young age at first intercourse, high numbers of sexual partners, high parity have consistently emerged as significant risk factors for cervical cancer [17, 18]. These, however, appear to be linked to sexual behavior and the acquisition of HPV; none being consistently shown as a significant independent risk factor [19].

The association noticed in this study between cervical cancer and socioeconomic deprivation most likely relates to poor cervical screening attendance, but also to unhealthy lifestyle. Income, education influence the access to appropriate early detection and treatment. Freeman described a model showing that health care disparities arise from a complex interplay of economic, social, and cultural factors [20]. On the other hand socioeconomic factors influence other risk factors for cancer, such as tobacco use, poor nutrition, physical inactivity, and obesity. Usually, poor and minority communities are targeted by the marketing strategies of tobacco companies, and they also may have limited access to healthy nutrition, or recreational physical activity.

Smoking has been identified as a HPV cofactor that might increase the risk for cervical cancer. Even if in our sample only around one third of patients were active current smokers, more than two thirds of them declared being exposed to other people tobacco smoke at home. In a pooled analysis of a 10 previously published case-control studies, eight case-control studies of invasive cervical carcinoma (ICC) and two of carcinoma in situ (CIS) from four continents [21] that used a similar protocol and included a PCR-based evaluation of HPV DNA in cytological smears or biopsy specimens, has been noticed an excess risk for ever smoking among HPV positive women. Analyze of results based on histological type, showed an excess risk among cases of squamous cell carcinoma for current smokers and ex-smokers. Even if tobacco smoke is a well-established Human Papillomavirus (HPV) cofactor for the development of cervical pre-cancer and cancer [22-24], the molecular mechanisms by which smoking increases the risk of cervical pre-cancer and cancer still remain unknown. Several plausible explanations have been postulated, including the inhibition of immune response to HPV by smoking, the DNA damage in carcinogenic HPV-infected cells exposed to smoking carcinogens. Also, it has been reported a molecular interaction between benzo[*a*]pyrene (BaP), a carcinogen found in cigarette smoke, and HPV synthesis, suggestive of yet another possible mechanism [24].

Evidence showed that long-term use of oral contraceptives (5 or more years) may be associated with an increased risk of cervical cancer [25, 26], but no long-term use of contraceptive was noticed in our sample of patients. A systematic review of the research has shown that women positive for HPV who have been used oral contraceptives for 10 or more years are 2.5 times as likely as never-users to develop cervical cancer [27].

In our sample obesity emerged as a major risk factor. In observational studies, obesity has been found as associated with cervical adenocarcinoma. It appears that through its hormonal actions, obesity might play a role in cervical adenocarcinoma pathogenesis, adipose tissue being an active endocrine and metabolic organ with possible far-reaching effects on the physiology of other tissues [28]. A systematic review and meta-analysis of articles that evaluated the relationship between body weight and cervical cancer in US [29] demonstrated a strong, graded, inverse relationship between BMI and the likelihood of undergoing screening for cervical cancer. Compared with their lean counterparts, women with class III obesity appeared around 40% less likely to undergo cervical cancer screening. Patients with obesity seem to avoid being Pap screened. Generally, obese women tend to delay medical care as a result of a negative self perception, associated with embarrassment, or because wanting to avoid weight loss advice [30, 31]. Obesity represents not only a risk factor, but also may affect prognosis through numerous pathways, including associated adverse disease features, co morbidities that can interfere with treatment, hormonal influences, and other mechanisms.

Conclusions

In our sample of patients, a high risk profile is taking shape for low socio-economical level, modulated by the impact of overweight-obesity, HPV infection with high risk stains of virus, smoking and inadequate cervical cancer screening.

In this frame, special alarms signal is represented by the very high percentage of patients with overweight and obesity. The key that connects obesity with cervical cancer appears to be largely the poor screening attendance by obese women. From the public health perspective, we consider that preventing weight gain could have multiple health benefits, including cancer risk decreasing and improving prognosis among those diagnosed, as obese people are not only more susceptible to cancer, but also have a significantly worse prognosis. In order to achieve this goal, concerted efforts of policymakers, physicians, schools and educators, to promote a healthy lifestyle are required.

Conflict of Interest

The authors declare that they have no conflict of interest.

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