The Epidemiology of Squamous Cell Carcinoma of the Uterine Cervix: Review of the Literature

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ABSTRACT Squamous cell carcinoma of the cervix represents the most frequent malignant neoplasm of the uterine cervix, consisting of squamous cells with malignant characteristics. The majority of squamous carcinomas of the cervix develop from lesions of the cervical epithelium, type CIN (cervical intraepithelial neoplasia) untreated after a varied period of time. Vast epidemiological studies proved that at a global level, cancer of the uterine cervix holds the second position as frequency, among tumoral pathology of female population and the third mortality cause. HPV represents the main risk factor involved in the occurrence of squamous cell carcinoma.

KEY WORDS carcinoma of the uterine cervix, Human papilloma virus, epidemiology

Introduction

Although, the uterine cervix can by easily the subject of a clinical examination, the cervical cancer holds the second position among the malignant neoplasm of the female population at the global level, after the breast cancer, representing 10% from all kinds of cancer [14]. In the developing countries (Africa, Latin America, Central and South-East Asia) the cancer of the uterine cervix holds the first position among malignant tumor pathology [6].

Recently, a decrease of incidence of the cervical cancer has been noticed in the developed countries, fact which underlines the success of the screening done for this neoplasia. The organizations involved in preventing the cervix cancer using screening programs have done epidemiological research studies regarding the incidence prevalence and mortality caused by cervix cancer [1, 8].

Incidence, prevalence, mortality

At the global level, the statistics reveal that 60,000 new cases are diagnosed every year and 30,000 females die due to the cervix cancer [8]. According to IARC (International Association for Cancer Research) in Europe during 2004, 34,300 females have been diagnosed and 16,300 females died due to this type of cancer [1]. This study has been performed in 27 states members of EU (European Union). Among EU members there are big differences regarding mortality, prevalence and incidence. These differences appear due to the way the screening programs are implemented, the mode the patients are monitored and treated and the level of information regarding this disease transmitted to the public.

Mortality indicates significant differences among the EU members. The highest mortality registered in Romania and Lituania, 13,7 and 10 per 100000 /year and the lowest mortality registered in Finland with 1,1/100000/ year [1]. In the states with the highest mortality, like Romania, screening programs are not applied and as a result the patients are diagnosed at a late status of the disease.

According to EUROCARE 3 study the 5 year survival rate for the cervix cancer diagnosed between 1990-1994 was 62% while for the cancer diagnosed between 2000-2004 the EUROCAR 4 study indicates a survival rate of 78% [16,18].
EUROCARE study is the most ample epidemiologic study done in Europe among the cancer survivors. This study has been implemented from 1990. The latest study, EUROCARE 4 includes data covering 93 cancer registers from 23 European countries. This percentage represents 13 millions people, approximately 35% of the population from the analyzed states [15]. EUROCARE 4 intends to become an information source for the cancer survivors from Europe and to underline the most important changes appeared in the analyzed states.

In 2006, in Romania 37,960 cervix cancer have been registered but our country was not included in the EUROCARE study due to fact that we do not have a national register for the patients affected by this disease [15]. The cervical cancer remained a serious problem of public health in the world and in Europe. At the global level the cervical cancer constitutes the second most common form of cancer, and in Europe it represents the seventh cause of mortality caused by cancer [9].

Risk factors

The cervix cancer is caused by a multitude of factors and its evolution is multistadial. The majority of squamous cell carcinomas of the cervix is evolving from preinvasive lesions of cervical epithelium (named CIN-cervical intraepithelial neoplasia) about 2/3 of the CIN untreated lesions evolving to invasive squamous cell carcinoma in a variable period of time estimated between 3 and 20 years [16]. Squamous cell carcinoma was rarely reported with a fast development, without preneoplastic lesions.

In the etiology of preinvasive lesions CIN, as well in squamous cell carcinoma are involved many factors as:

Determinative factors are defined from epidemiologic point of view as being the factors which are preparing, weakening and creating a specific status at the uterine cervix, status which forces the cervix to react.

Human papilloma virus (HPV) is one of the above mentioned factors, being recognized as a major risk factor in pathogenesis of squamous cell carcinoma of the cervix. A link between the HPV and the presence of the cervix cancer has been documented, the HPV being a major risk factor in the development of preneoplastic lesions and directly in the development of squamous cell carcinoma. This connection between HPV infection and squamous cell carcinoma is sustained by numerous molecular and laboratory studies which revealed the presence of the HPV DNA in 90% of the invasive squamous cell carcinoma [3,5]. Many of the HPV infections documented among the young females are temporary and do not present significance for long time, 70% being cured in the first year and 90% in the second year. Only a small percentage, 5-10% from the females infected with HPV is expected to develop a persistent infection [11].

HPV has been classified after the oncogenic risk as:

- HPV with low oncogenic risk (HPV-LR) with types 6, 11, 42, 43, 44, 53. Type 6 and type 11 are associated with condylomas, occasionally with low grade intraepithelial lesions (LSIL) and exceptionally with high grade intraepithelial lesions (HSIL) and never with squamous cell carcinomas. Types 43, 44, 53, 61, 70, 72, 81 of HPV are rarely present by their distribution of lesions are similar with type 6 and 11.

- HPV with high oncogenic risk (HPV-HR) with types 16, 18, 45, 46, 56, 58 are associated with squamous cell carcinoma. Recently, other types of HPV like types 31, 33, 35, 39, 51, 52, 59, 68, 73 and 83 have been identified in invasive squamous cell carcinoma [12].

Associated factors (cofactors) are the factors which contribute to progression of disease.

The most important are:

- The virus herpes simplex type 2 (HVS type 2). The infections with this virus are part of sexually transmitted diseases. Occasionally, particles from HPV genome were identified in squamous cell carcinoma cells, suggesting a possible interaction between HPV-HR and HVS type 2, as well their involvement in the development of squamous cell carcinoma. The patients having antibody against HVS type 2 and positive DNA for HPV 16 and 18 have a double risk in developing an invasive squamous cell carcinoma [10].

- The human immunodeficiency virus (HIV). The patients infected with HIV have a deteriorated immunologic status, so the females HIV positive have a higher risk in contacting a large number of microorganisms, part of them being HPV-HR which could lead comparing to the females with HIV negative. Recent studies regarding female population from developing states, indicates that the value of the associated rate of HPV infection with HIV is 4,4. The female infected with HIV and HPV-HR have a risk 40 times higher in developing squamous cell carcinoma [13].

- Related to the role of smoking in the occurrence of squamous cell carcinoma there are many hypotheses. At the level of the cervix of the cervix mucus have been identified some substances like nicotine and cotidine in higher
concentration then in serum. Those chemical carcinogens cause structural alterations of the cells DNA from the cervical epithelium [17]. As well the relation smoking-squamous cell carcinoma could lead to the occurrence of a cervical immune answer, the smoking females presenting a lower number of Langerhans cells which are responsible in local immune protection. This decrease of local immunity determines an easier infection with various viruses, especially with HPV [2].

The using of combined hormonal contraceptives is as well brought to attention as being a possible risk factor involved in occurrence of squamous cell carcinoma, but this association is less evident if we take in consideration the detection of HPV. Studies done regarding this matter revealed that the females using oral contraceptives have a faster progression of the preneoplastic lesions of squamous cell, so, the usage of contraceptives plays a major role in fastening the progression of the disease.

The lack of A and C vitamins in the food and deficiency of folate. Some studies revealed that the females diagnosed with CIN and squamous cell carcinoma had the folate level under 660nmol/l, as well deficiency of A and C vitamins and, more important they were HPV 16 positive [4].

Various researches done over the least years show that HPV is the major risk factor in developing precursor lesions and squamous cell carcinoma. Aside HPV are other operational factors but we can discuss about other aspects or associated factors involved in the etiology of squamous cell carcinoma:

- early debut of sexual life (under 17 years) with multiple sexual partners, high parity, repeated abortions causing repeated traumas of the cervix which increases the possibility of transmission of microorganisms some of them with oncogenic potential like HPV.

- deficiency of genital hygiene-smegma could be considered having a potential carcinogen factor.

- low socio-economical conditions and environmental factors.

- genetic factors: the majority of squamous cell carcinoma is determined by a preferential group of risk factors and involves a specific way of occurrence. A reduced number of cervical cancers are caused by risk factors determining similar or different genetic modifications no matter the order of the events. Cellular immortalization which is an early event of cervical carcinogenesis is due to the cooperation of different risk factors which could determine independently or simultaneously the conversion of the proto-oncogene in oncogenes or/and the inactivation of the antioncogenes [7].

**Conclusions**

The cervical cancer remains a serious problem of the public health all over the world, in Europe and Romania, problem which has been solved by implementing efficaciously screening programs and vaccination programs against HPV-HR. The majorities of squamous cell carcinomas are determined by preferential groups of risk factors and present a specific way of events in their development. The appearance risk of squamous cell carcinoma is firstly connected to sexual transmitted factors (especially HPV-HR infection), the rest of the risk factors like smoking, diet, hormones being additional to these.

**References**

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