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CERVICAL CANCER – ETIOLOGY, PREVENTION, INTERVENTION AND THERAPY

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Abstract
Cervical cancer (CC) is the second leading cause of cancer morbidity and mortality around the world. The development of CC involves major factors as the infection with high-risk human papillomavirus (HPV), estrogen imbalance, high sexual activities and cigarette smoking. Knowledge of the categories of risk factors is used to develop prevention strategies for CC, of major interest being the metabolism of environmental chemicals that contain carcinogens, such as in cigarette smoking. The most important strategy could be the reduction of the ackuired risk factors to CC such as modification of sexual activities in order to reduce infection with high risk HPV and quitting the cigarette smoking habit. Implementation of these modification need to be adjusted according local population, taking into account the different impact of risk factors to different population, as our research has shown. The development of vaccine to prevent infection and therefore CC is a major world-wide effort.

Key words: cervical cancer, high-risk human papillomavirus (HPV), carcinogens,cigarete smoke-specific DNA, oxidation reaction.

Rezumat:
Cancerul cervical (CC) este a doua cauză de morbiditate şi mortalitate prin cancer în lume. Dezvoltarea CC este influenţată de factori majori, cum sunt infecţia cu virusul uman papilloma, dezechilibrul estrogenic, activitatea sexulă crescută şi fumat. Cunoaşterea categoriilor de factori de risc este utilă în dezvoltarea strategiilor de prevenţie pentru CC, de un interes major fiind metabolismul substanţelor chimice carcinogene din mediu, aşa cum sunt în fumul de ţigară. Cea mai importantă strategie ar putea fi reducerea factorilor de risc care contribuie la dezvoltarea CC, cum ar fi modificarea activitaţii sexuale în vederea reduceriiinfecţiei cu virusul uman papilloma şi renunţarea la fumat. Implementarea acestor modificări necesită standardizarea la nivelul populaţional, luînd în consideraţie diferenţele de impact al factorilor de risc în populaţii diferite, aşa după cum au arătat cercetările noastre. Un efort major la nivel mondial îl constituie dezvoltarea unui vaccin pentru prevenirea infecţiei, şi astfel a CC.

Cuvinte cheie: cancer cervical, virusul uman la risc înalt papilloma, carcinogene, ADN specific din fumul de ţigară, reacţii de oxidare.

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RISK FACTORS FOR CERVICAL CANCER

Cervical cancer (CC) is the second leading cause of cancer morbidity and mortality among women around the world.(1). More than 200,000 deaths are registered each year. The mortality predominantly impacts the economically disadvantaged women in both developing and industrialized nations (2). Infection with high-risk human papillomavirus (HPV) has been identified as a "necessary cause" for CC (3). However, most HPV-infected women do not develop CC as infection is frequently found in asymptomatic individuals (4). Therefore, additional risk factors are needed for the initiation and promotion of cervical carcinogenesis (5).

As HPV infection is considered a sexually transmitted disease, investigations to reveal sexual behavioral risk factors have been conducted (6,7). Overall, women who had first sexual intercourse at an early age or who have had many sexual partners have an increased risk of developing CC. In addition, the presence of other sexually transmitted diseases may enhance the risk for CC.

Another contributing risk factor is exposure to estrogen because cancer risk is increased 2 – 4 times for women with extended use of oral contraceptives and 4 times for women having more than 7 children

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(8). Although estrogen is classified as a human carcinogen for a variety of cancers, its effectiveness for the induction of CC is through interaction with HPV since very few CC are free from HPV infection (9).

Cigarette smoking has also been reported to be an environmental risk factor for CC (10,11). Epidemiological studies have shown that the risk for neoplasia increases with longer duration and intensity of smoking (12). The presence of cigarette-derived chemicals such as nicotine, cotinine, and N-nitrosamines in cervical mucus and cigarette smoke-specific DNA adducts in cervical epithelial cells provide further support for the contribution of cigarette smoking to CC (13,14,15,16,17). Although these factors are now considered as surrogates of HPV exposure or as cofactors given the presence of HPV, their contribution to cervical carcinogenesis may vary between different geographic regions, and therefore, it should be investigated (3).

SUSCEPTIBILITY TO CERVICAL CANCER

It is now well-established that several environmental and life-style factors are involved with the development of CC. They are infection with high risk HPV, estrogen imbalance, high sexual activities and cigarette smoking. However, it is also clear that many

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females with the combination of the risk factors do not develop CC. This phenomenon in CC and in other cancers stimulated an intense interest in elucidating susceptibility factors for disease. One major interest is concentrated on the metabolism of environmental chemicals that contain carcinogens, such as in cigarette smoke.

It is well-known that most cigarette smoke procarcinogens need metabolic activation in order to exert their carcinogenic effect (18). Therefore, genetic differences in the metabolism of cigarette smoke may determine individual predisposition to CC. Cytochrome P450 (CYP) comprises the principal enzyme system catalyzing various phase I oxidation reactions of xenobiotics including the metabolic activation of carcinogens (19). CYP2E1 is known to metabolize several tobacco-smoke carcinogens, including N-nitrosamines, benzene, styrenes, butadiene, and urethane (20). A genetic polymorphism in the 5'-flanking region of CYP2E1 causes increased enzyme activity, and thus, an enhanced ability to activate certain chemicals (21). This genetic polymorphism has been associated with the development of lung cancer and nasopharyngeal carcinoma (22,23,24).

Microsomal epoxide hydrolase (mEH) is a key participant in chemical detoxification pathways, catalyzing the hydrolysis of reactive aliphatic and arene epoxides

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generated by cytochrome P450 enzymes to more water-soluble dihydrodiol derivatives (25). Although it is considered a detoxifying enzyme, mEH contributes to the bioactivation of benzo[a]pyrene, a cigarette smoke constituent, to the highly carcinogenic benzo[a]pyrene-diolepoxide (26). Interindividual differences in mEH activity ranging in scale from several to 40-fold can be attributed to genetic polymorphisms at two residue positions within the coding region of the gene: residue 113 Tyr/Hist and residue 139 Arg/Hist (27,28). Substitution at residue 113 has been shown to decrease mEH activity by approximately 40% (28). The His-113 allele has been associated with an increased risk for hepatocellular carcinoma and chronic obstructive pulmonary disease, and has also been associated with a decrease in risk for lung cancer (29,30,31). Conflicting results have been reported for ovarian cancer and the Tyr-113 allele (32,33).

Among the phase II enzyme detoxification systems, glutathione S-transferase mu (GSTM1) catalyzes the conjugation of reduced glutathione to a variety of electrophilic compounds, including metabolites of several chemicals in cigarette smoke.(34). GSTM1 has an allelic variant *0 (null allele) that causes lack of enzyme activity in the homozygous form(35). This is associated with reduced efficiency in

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binding genotoxic substrates, including epoxides deriving from polycyclic aromatic hydrocarbons (PAHs) and aflatoxin(34). Epidemiological studies have shown that homozygous null individuals have an increased risk for cancer at a number of sites, including bladder, skin, colon, lung, breast, and ovary(20,23,36,37,38,39).

We have conducted a molecular epidemiology study in the US to determine if inheritance of variant metabolizing genes may be involved in risk for CC (40). From our study, a significant increase in risk for neoplasia was observed for the low activity mEH 113 His allele after adjustment for smoking (OR = 3.0, 95% CI = 1.4-6.3). The GSTM1 null genotype was associated with a significant 3.3-fold increased risk for neoplasia (95% CI = 1.0-11.8) compared to women who were GSTM1 positive, after adjustment for smoking and HPV infection. Our study suggests that genetic differences in the metabolism of cigarette smoke confer susceptibility to CC.

PREVENTION OF CERVICAL CANCER

With knowledge from our study and from the literature, it is clear that the development of CC involves three major factors and the most important factor is infection with high risk HPV. A summary of this knowledge is shown in Figure 1.

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Knowledge from the first three categories in the figure is used to develop prevention strategies for CC. One approach is to modify life-style to reduce the acquired risk factors to CC such as modification of sexual activities to reduce infection with high risk HPV and quitting the cigarette smoking habit.

Uniform implementation of such life style modification program to all countries in the world may not necessarily generate the same level of success. One reason is that the risk factors for CC may have different impact to different populations as we have observed in Venezuela and in the US (40,42). HPV infection was significantly associated with CC for both populations as expected, but the Venezuelan controls were twice as likely to be infected with HPV as the US controls. Having > 2 lifetime sexual partners (OR = 6.4, 95% CI = 2.7-15.0) and initiation of sexual activities before the age of 18 (OR = 4.4, 95% CI = 1.8-10.8) were significant risk factors in a multivariate model for CC in Venezuela but not as significant in the US. In contrast, current cigarette smoking was a significant risk factor only in the U.S. (OR = 3.6, 95% CI = 1.7-7.7). Therefore, different emphasis and use of resources may be considered for different populations for an effective prevention of CC.

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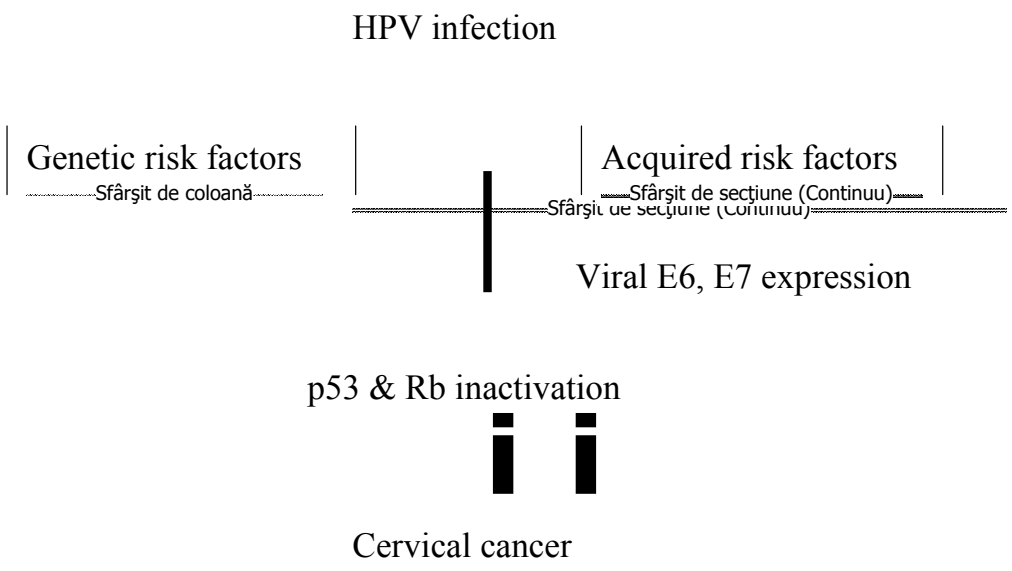
Fig.1: Diagrammatic illustration of the etiology for cervical cancer.



The development of vaccine to prevent infection and CC is a major world-wide effort. Some vaccines have shown promising results in reducing CC among high risk populations (41).

INTERVENTION AND GENE THERAPY APPROACHES

Use of knowledge in the genetic susceptibility category is promising in preventing and intervening CC among those who have heritable susceptibility to the disease. A possibility in the future is in the use of gene therapy to correct the defective gene. However, more definitive knowledge regarding the genetic susceptibility is needed before this approach can be initiated. On the other hand, the development of novel gene therapy protocols is ongoing and these protocols are focused onto the biochemical and molecular pathways that are well-characterized. As shown in Figure 1, the primary oncogenic mechanism of HPV is the release of viral E6 and E7 proteins that bind and inhibit the function of cellular tumor suppressor genes, p53 and pRb, respectively. The inhibition of the two tumor suppressor genes is supposed to allow cells having genomic damage to survive and to evolve into cancer cells. Thus, blocking of the expression of the viral E6 and E7 genes is potentially a powerful tool to interrupt the oncogenic effect of HPV. This can lead to the termination of the cancer process and to the initiation of self-destruction of the cancer cells (5,42). A molecular blocker that is highly precise and effective is the small interference RNA (siRNA). The gene therapy approach is precise and can be used as a non-surgical procedure to eradiate cancer. The approach is in fact becoming a clinical reality in modern medicine.

CONCLUSION

In the field of public health and oncology, it is critical that sufficient effort is applied to the characterization of the causation and mechanism of development of cancer. In addition, such knowledge needs to be developed for each population because there are significant variations from one to another population. The availability of such knowledge opens up many opportunities for effective eradication of cancer through targeted prevention, intervention and therapy programs.

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