

Modern look to the risk factors and prevention of cervical cancer

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Abstract

An analytical review of research in the field of epidemiology and carcinogenesis of cervical cancer and measures and technologies for the prevention of this form of cancer has been carried out. There are considered data on the main proven risk factors for cervical cancer, which are as follows: certain characteristics of sexual behavior and reproductive history, sexual infections and infection with human papillomavirus (HPV), tobacco smoking and some other lifestyle characteristics. According to world reference data the analysis of existing methods of cervical cancer prevention including sanitation, HPV vaccination and various types of screening for cervical cancer was conducted. Data on the significance, effectiveness and availability of various preventive technologies are presented.

Key words: cervical cancer; reproductive history; human papillomavirus; tobacco smoking; prevention; sanitation; vaccination; screening.

Cervical cancer (CC) is one of the most common forms of malignancies in women. In the structure of cancer morbidity and mortality among women worldwide, CC ranks third and fourth, respectively, accounting for 9% (529800) of all new cancer cases and 8% (275100) of all cancer deaths among women in 2008 [7]. The incidence of CC varies markedly across regions and countries of the world. Some countries in Asia, South America, and sub-Saharan Africa have the highest standard incidence of CC, at least 41 per 100,000 populations. The lowest incidence of CC is found in China, Israel, Turkey, where the standardized incidence rates are only 2-4 cases per 100,000 women population. In Ukraine, the standardized (world standard) incidence rate of

CC is 15.3 per 100 000 women [2]. In the morbidity structure of the female population of Ukraine in 2013, CC was 5.3% and took sixth place. In the age group of women under 29 years of age, CC ranks first among the female population, accounting for 12.5% [5].

Long-term and numerous studies on the epidemiology and etiology of CC have revealed a complex of risk factors that can participate to some extent in the process of carcinogenesis of CC and determine the probability of its development. Diethylstilbestrol (prenatal exposure to the hormone in the womb) is a proven carcinogen for humans, particularly in relation to the development of DSM, estrogen-progestogen contraceptives, human immunodeficiency virus (HIV), genotype 1, human papillomavirus (HPV), genotypes 16, 18, 31, 33, 35, 39.45, 51, 52, 56, 58, 59, smoking tobacco [2]. There are more numerous so-called risk factors, which are not carcinogenic but can play a promotion role in the development of CC. Based on the analysis of more than 100 analytical studies on the epidemiology of CC, the following groups of risk factors were identified, in respect of which a number of studies have shown a statistically reliable connection with CC risk: socio-demographic (age, educational level); lifestyle factors (diet, smoking status, individual hygiene); sexual behavior (number of sexual partners, number of marriages, age at first marriage); reproductive history (age at first pregnancy).

Historically, a link was established between the risk of CC development and certain characteristics of sexual behavior, reproductive and gynecological anamnesis. A number of analytical studies have established a statistically reliable connection between the risk of development of CC and the early age of sexual life. In particular, it has been shown that the risk of developing CC is twice as high at the beginning of sexual life of women before the age of 15 compared to women who started sexual life from the age of 19 and later [8]. According to another study, the interval between menarche and first sexual intercourse < 6 years of age resulted in a 3-4-fold increase in the relative risk (RR) of developing CC. Based on the results of a multifactor analysis of the data from two case-control studies in Israel, the authors conclude that late age of sexual debut is a protective factor in relation to CC. It has also been found that the absence of sexual activity in a woman's history significantly reduces the risk of flat cell CC [9]. In population studies, it was found that CC is extremely rare in virgins, and rare cases of CC in virgins are glandular cancer and almost never flat cell cancer [1]. The etiopathogenetic importance of early sexual initiation is explained by the fact that at the age of 12-15 years the immature epithelium of ectocervicals is more sensitive to the influence of carcinogens and co-carcinogens [9]. In addition, onset of sexual activity before age 16 was found to significantly increase the probability of HPV infection, with a probability ratio (OR) of 4.41; 95% confidence interval (DI): 1.20-19.33; p=0.01).

Several studies have found a significant link between the risk of CC and an increase in the number of sexual partners, irrespective of the age at which sexual activity begins [9]. The large number of sexual partners is known to be a significant risk factor for HPV infection, and is now recognized as the main carcinogenic risk factor for CC. Therefore, a special meta-analysis of 41 relevant studies assessed the relationship of the number of sexual partners controlled by the HPV infection factor. The results showed that, irrespective of HPV infection, the history of more than 4-7 sexual partners significantly increased the risk of CC (OR=1.53, 95% of DI 1.30-1.76). It has also been found that the risk of developing CC over life is almost twice as high in women who become pregnant at age 17 and earlier than in women whose first pregnancy was 25 years old or older [9]. Other analytical studies have found a significant increase in the risk of CC in women with more than four births in the history, especially if delivery was accompanied by cervical ruptures with subsequent scarring.

A number of studies have shown that the risk of developing CC increases the long-term use of hormonal contraceptives. In 2007, the International Agency for Research on Cancer conducted a meta-analysis of 24 studies on the relationship between oral hormonal contraceptive use (OHC) and the risk of developing CC. Data were used on 1,573 patients diagnosed with CC and 3,509 women without oncopathology. The results of a certain analysis showed that the risk of invasive cancers increases with increasing duration of OC use. Thus, among women who had used OC for 5 years or more, the risk of CC was almost twice as high compared to women who had never used OC. At the same time, the relative risk of developing CC increases with the continuation and duration of OC use and decreases after their withdrawal. In order to assess the association of OC intake with the risk of CC, a survey was conducted in Korea of 678 women infected with HPV infection. Of these, 367 women were found to have cervical intraepithelial neoplasia (CIN) of varying degrees and 411 to have no pathological changes in the cervix. Analysis of the relationship of pre-tumor dysplasia in the cervix with OC showed a significant increase in the probability of CIN 2-3 for all users of OC compared to non-OCs, OR = 1.98; 95% DI, 1.07-3.69, with OR = 2.71; 95% DI, 1.11-6.59, compared to non-OCs. In another study comparing two groups of women who had been using hormonal contraceptives for 10 years or more and who had never used a contraceptive, it was found that the probability of developing CC in the first group increased almost 2.5 times compared to the second group of women, OR=2.42, 95% DI - 1.13-5.15 [15].

With regard to the impact of hormones on the risk of CC, it should be emphasized that prenatal exposure to diethylstilbestrol as a result of taking this hormone drugs by mothers during pregnancy may also significantly increase the risk of CIN3 and CC development in daughters,

and at the age of 45 years, in older age, the presence of this factor did not increase the risk of disease.

Sexual infections, primarily viral etiology, are one of the main proven risk factors for CC. Thus, the herpes simplex virus (HPV) of the second type and the cytomegalovirus may play a role in the development of CC. The main role in the process of carcinogenesis of CC is played by human papillomavirus (HPV), especially by 16 and 18 types, and also by 31 and 33 types [6]. Professor H. Zur Hausen (1974, 1985) first suggested, and later confirmed, the etiological connection between HPV and CC by establishing the integration of HPV into cell DNA in CIN and CC cells. In almost all subsequent case-control studies, a link was also established between the presence of HPV DNA in cervical cells and the risk of CIN and CC. The presence of HPV DNA in cervical DNA cells was found in 90% or more of all cases of precancerous lesions and CC. Another study found that 81% of women with CIN2-3 had HPV infection, while only 21% of women with normal cervical cytology had HPV infection. Popular and cohort studies have shown that HPV prevalence always correlates with increased CIN frequency. Summarizing the data of the corresponding studies, it can be considered that the carriage of HPV infection increases the risk of cervical cancer by a factor of 10 and more times [4], and HPV infection is now recognized as the most significant factor in the carcinogenesis of cervical cancer [2]. In a biopsy study of women with early stage CC, HPV infection was detected in 95.8% (92/96) of patients. The most common genotypes were HPV 16 (59.4%) and HPV 18 (60.4%). In another study involving 2,507 women diagnosed with CIN or CC in situ, infection with different HPV genotypes was found in different groups of patients within the following ranges: with CIN 1 in 43%-55% of cases, with CIN2 in 70%-78%, with CIN3 in 85%-91%, with RM in situ in 95%-100%. Thus, it has been established that with progress in neoplasia in the cervix, the proportion of people infected with HPV will increase markedly. Recently, there has been evidence that there is a less pronounced etiological link between HPV infection and the development of CC. In particular, a study conducted in Iran examined 123 women with a verified diagnosis of CC and 100 control women without cervical pathology for HPV infection. HPV infection, most commonly genotypes 16 and 18, was found in 34.2 per cent of CC patients and 12 per cent of those in the control group. The authors note that although the prevalence of HPV in the control group of CC patients was markedly higher than in the control group, the direct link between CC and HPV infection in this study was significantly weaker than in many other relevant studies, which, in the authors' opinion, may be due to the more significant role of other risk factors in the carcinogenesis of CC in this region. In one Ukrainian study, 270 women were examined for HPV, including groups of women with various diseases. The most frequent cases of infection with different types of HPV were found in CC patient groups (30%) and with 3rd degree CIN

(33.3%), while in other patient groups the presence of HPV was significantly lower: 15% for CC, 10% for RE, 9% for CIN 1-2 degree, and 2.5% for women with no tumor diseases. The frequency of HPV detection in women with CC and CIN 3 was statistically significantly higher than in other groups of women, with p ranging from 0.05 to 0.001 [3]. In another study, 456 (98.7%) of 462 patients with a verified diagnosis of CC were found to have HPV infection. The most common genotypes were: HPV16 (46.5%), HPV18 (10.4%), HPV45 (6.7%), and HPV31 (4.1%).

The data showed that young women with CC in most cases had high carcinogenic risk HPV genotypes, while half of the older patients were more likely to have low carcinogenic risk HPV genotypes, which suggests that other risk factors for CC in older age groups are involved. Screening for HPV infection data from about 41000 women aged ≥ 25 years have been analyzed by American researchers. The most frequently identified HPV genotype was 16, in the 25-29 and ≥ 50 age groups, with infection rates of 3.5% and 0.8% respectively. Among women with \geq CIN3, HPV 16 and HPV 18 were found in 45.6% and 8.4% of individuals, respectively. The authors believe that HPV 16 plays a leading role in \geq CIN3 development, regardless of age. Therefore, identification of HPV 16 is recommended in the initial screening of all women.

HPV infection is considered by most researchers to be a prerequisite for the development of the CC. However, damage caused by the virus alone is not sufficient for the development of CC, which may be due to the existence of additional factors that may be involved in the carcinogenesis process [14]. The development and consolidation of the infection is facilitated by a decrease in the immune status. Both of these risk factors for CC are closely interconnected. In particular, it has been found that the risk of developing CC is significantly increased in women with reduced immunity due to AIDS or after organ transplantation therapy, as well as in patients with terminal renal failure and in some autoimmune diseases. Evidence has been obtained that the combination of HPV with bacterial infection, primarily gonorrhea and trichamatus infection in the cervix, significantly increases the risk of precancerous and initial cervical cancer changes. These data indicate a possible role of bacterial infection as a significant cofactor in HPV mediated carcinogenesis [11].

Tobacco is the most common of the proven carcinogens for humans. A direct causal relationship of tobacco smoking (TS) with 15 forms of malignance, including CC, has been proved [2]. In a number of epidemiological analytical studies, TS has been found to have a significant effect on the risk of developing CC. First of all, it has been found that the spread of TS has been twice or more higher among CC patients than among women in a population or A fairly extensive case-control study in Finland, involving 588 CC patients and 2861 women in a selected control group, through multifactor analysis of other factors that may influence the risk

of CC, has established that TC is an independent risk factor for CC, including in the HPV-infected female population. Another study included 609 women with CIN 3 and CC and 1,218 women in the control group. All women completed special questionnaires and also took blood for PCR diagnosis of HPV 11, 16, 18, 31, 33, 35, 45, 52, 58 types. The multivariate analysis also showed that TS, irrespective of other factors, including HPV infection, significantly increases the risk of developing SC, which increases with the intensity and duration of TS. At the same time, when TC was discontinued, this risk decreased. The data from the Ukrainian study are very revealing, given that the spread of TS among the population in Ukraine is one of the highest in the world. The studied cohort of women, with a total number of 278 people, included 6 groups, comparable in age and social status, but with different diagnoses. The percentage of smokers was 43.8% in the CC group, 45% in the 3rd degree CIN group, 9% in the 1st-2nd degree CIN group, 4.2% in the endometrial cancer group, 12% in the breast cancer group, and 1.9% in the healthy group. Thus, the percentage of smokers was several times higher among women with CC and CIN 3 degree compared to the group with CIN 1-2 and control groups without cervical pathology. The corresponding differences were statistically significant - p ranged from 0.001 to 0.05 [3]. In a prospective study conducted in Japan, 516 women with CIN 1 were monitored, and every 4 months they underwent a cervical smear and colposcopy cytological examination. The average follow-up period was 39.8 months. The results of the observation showed that after two years the probability of regression of lesions and restoration of normal cytology was significantly lower in smokers compared to non-smokers, 55.0% and 68.8%, respectively, $p=0.004$. At the same time, it was found that in the group of smokers' patients, CIN resistance during observation increased with increasing intensity and duration of TS, i.e. TS significantly increases the risk of cervical resistance development [16]. In Portland, USA, a 10-year prospective study was conducted on 1,812 women who were found to have HPV infection at the start of the study. All cases of CIN 3rd degree and CC were observed in this cohort. A final multifactor analysis, taking into account all factors that may affect the risk of CC, showed increases in CIN 3 and CC. Those who smoked in the past, smoked less than a pack per day and smoked more than a pack per day compared to those who had never smoked had CC of 2.9 (95% CI 1.4-6.1), -3.3 (95% CI 1.6-6.7) and 4.3 (CI=2.0-9.3) respectively.

The results of an experimental study in which cervical epithelium with integrated HPV genomes of 16 or 31 types in experimental animals was treated with tobacco smoke condensate are very indicative. Exposure to tobacco smoke condensate caused dose-dependent increase in viral replication of the genome and, consequently, higher rate of gene transcription in HPV-infected cells. These data suggest that tobacco smoke plays a significant role in the progression of the early stages of CC associated with HPV. Another study found that tobacco compounds can

be secreted by glands in the cervical canal. In women who smoke, nicotine is 100% present in cervical mucus and 84% in cervical mucus, while in non-smoking women, these compounds were absent in cervical mucus. A number of studies have confirmed a dose-dependent connection between the risk of CC and TS, i.e., the risk of CC development has increased with increasing intensity and duration of TC. A number of studies have investigated the possibility of influence of so-called passive or secondary smoking, i.e. passive exposure to tobacco smoke from non-smokers' environment, on the risk of development of CC. It has been found that the risk of developing CC in women who have never smoked has increased significantly if their husbands, sexual partners or close people were smokers. At the same time, the risk of developing a CC among non-smoking women was significantly related to the intensity and duration of close people's TS. It is indicative that analysis of mucus taken from the cervical canal in women exposed to passive TS showed a significant increase in the levels of non-metabolized coning and nicotine. All these data indicate that not only active TS, but also passive exposure to tobacco smoke can significantly increase the risk of developing CC in non-smoking women.

Certain background or benign pre-tumor changes in the cervix should also be considered as risk factors for CC, in which the probability of CC development is significantly increased. Generally, background and precancerous changes in the cervix precede the development of cancer, which rarely occurs in the unchanged epithelium of the cervix. Cervical background processes include polyps, leukoplakia, true erosion, pseudoerosion and flat condylomas. Pre-cancerous processes include dysplastic changes in the flat epithelium of the cervix, in particular, CIN of different degrees of severity [16]. The weak degree of dysplasia (CIN I) in most cases regress spontaneously, and in moderate degree (CIN II) and severe degree (CIN III) dysplasia, respectively, in 5% and 12% of patients progress into invasive cancer. The risk of progression increases primarily when HPV infection is present. Therefore, estimating the quantitative load, physical status of the virus, and its genotype can serve as a marker for predicting the course of CIN.

There are factors not of direct carcinogenic effect, but cofactors or promoters of the carcinogenesis process, which may significantly affect the risk of developing certain forms of CC. Thus, multifactor case-control studies have shown that the risk of CIN3 and CC significantly increases with age and in the presence of long-term depression and anxiety [12]. Some countries have seen an increase in the incidence of RMVs in rural areas with no or a decrease in the incidence in the urban population. Multi-factor analysis by Indian researchers has shown that two factors, poor sexual hygiene and low socioeconomic status, can statistically increase cervical cancer risk independently of other factors. Another study showed that among women infected with HPV and who consume alcohol for long periods and at high doses, the risk

of cervical pre-tumor dysplasia development and persistence was significantly higher than among comparable groups of women who consumed little or no alcohol [19]. A dietary factor study showed that the so-called "semi-western" diet, characterized by high levels of bread, dairy products, eggs and fats, was associated with a significantly higher risk of CIN development compared to other more stringent and healthy diets, OR= 3.44, 95% DI 1.11-10.7, p = 0.03). In the USA, a case-control study was carried out, which included 128 patients with CC and age-matched controls - 512 women without pathology in the cervix, in the examined women physical activity throughout their lives was assessed by a specially developed method. The results of the study showed that women with CC were significantly more likely to note absence of significant physical activity and abstinence from physical activity in comparison with women of the control group, OR= 2.43; 95% of DI, 1.56-3.80.

Interaction of risk factors at CC

The multifactor etiology of CC explains the relative rarity of CC in the presence of a single risk factor even such as HPV infection, which is found in the vast majority of already sick CC. However, among HPV-infected healthy women, at the same time, herringbone marrow disease is very rare. Moreover, most women have spontaneous regression of HPV infection, and only a small proportion of those with persistent HPV infection develop CC. Several factors of carcinogens or co carcinogens and promoters are needed to develop the clinical stage of CC. In this case, a combination of some risk factors in the history may have a synergistic effect, i.e. their effect on the risk of disease development is not easily summarized, but multiplied. It is important to take such combinations of risk factors into account when selecting risk groups, in particular, in relation to CC. Thus, a number of studies have shown that among women infected with HPV, the presence of TS in the history significantly increases the risk of development of CC compared to women who have never smoked with HPV, i.e. a potentate and multiplicative effect has been established with the combined effect of TS and HPV on the risk of development of CC [3]. One analytical epidemiological study showed that the combination of TS with a diet characterized by low consumption of fresh fruits and vegetables reliably increased the risk of CIN 3 almost fourfold. Another study found synergies in acting on the risk of cervical pre-tumor changes between two factors, HPV infection and alcohol consumption at relatively high doses and over a long period of time [19]. In a Korean study covering 678 HPV-infected women (411 healthy, 133 with CIN 1, and 134 with CIN 2-3), it was shown that combinations of factors such as TS and OC are more likely to produce cervical pre-tumor changes than each of these factors separately. Thus, the presence of a combination of TS and OC in the anamnesis increased the probability of CIN 2-3 by a factor of almost 5 (OR 4.91; 95% CI, 1.68-14.4), and with TS more

than 8 cigarettes per day and OC more than 20 months. - almost 12 times (OR 11.5; 95% CI, 1.88-70.4) compared to non-smokers and non-OC users.

The prevention of CC is based on a strategy to identify factors that significantly affect the risk of occurrence of CC, to assess the potential for correction with respect to these factors and to introduce into public health practice acceptable methods to eliminate or neutralize these risk factors [4]. In order to prevent CC, several preventive technologies have been investigated, tested and, to varying degrees, implemented and have proven to be effective. The fundamental technology that largely determines the "preventive behavior" of women and the effectiveness of other technologies is to educate the public about scientifically proven risk factors of CC and methods of their elimination or correction, either on their own or under the control of a physician. This training for women should be provided by doctors at the primary level of the health-care system, and above all by gynecologists and obstetricians. Depending on conditions and possibilities, different forms of health education should be used: information and recommendations from a doctor, distribution of thematic leaflets on prevention of CC, holding thematic discussions and lectures in teams, etc. CC prevention education for women is especially relevant and of paramount importance in relatively underdeveloped countries, where low level of knowledge about risk factors and opportunities for CC prevention is the main obstacle to CC prevention among the population. However, in more developed countries as well, certain surveys indicate that there is a need for appropriate training for the female population. For example, Polish researchers surveying women to determine their knowledge of CC risk factors found that 26% of those surveyed could not name a single CC risk factor. In another region, a survey found that 68% of women had never heard of HPV, but of those who had received the information, more than 90% were interested in being vaccinated against HPV. Today, CC can be effectively prevented by existing effective prevention measures. But their effective use and women's consent depends above all on women's awareness of these measures and their capabilities.

To date, HPV vaccination has been recognized as the most effective method of preventing CC. However, in order to determine the extent of vaccination coverage of the female population, vaccination regimes, in which groups it is most shown, the peculiarities of HPV infection spread in a particular region and population should be taken into account. HPV infection prevalence and incidence of different genotypes may vary significantly between geographical and ethnic populations, and among different age groups in the female population. For example, a study of 555 women aged 18-75 in Guangdong Province, China, found HPV infection in 7.3% of the women surveyed; in Bahrain, HPV infection was found in 9.8% of women, with the most common genotypes being -52, -16, -31, -51, -6. In another population study involving more than 12 000 women aged 15-45 years, the presence of persistent HPV

infection was found in 29% of women in the 15-26 age groups, in 12% of women aged 24-34 years, and only 6% of women aged 35-45 years. HPV infection is most prevalent among the population in some African countries and also in Australia among the indigenous population, where 66.3% of women fewer than 21 years of age have HPV, and 15.3% of women after 40 years of age have HPV. A significant increase in the sexual activity of young people, especially adolescents, is believed to be one of the main reasons for the high prevalence of HPV infection in populations [18].

As a result of the introduction of basic and epidemiological research on carcinogenicity of HPV, three vaccines have been created, tested, licensed and recommended for use to prevent HPV infection and ultimately prevention of CC:

- bivalent vaccine against HPV16 and HPV18
- quadrivalent HPV vaccine 6, 11, 16, 18
- 9-valent HPV vaccine
6/11/16/18/31/33/45/52/58.

The most widely used bivalent vaccine protects against type 16 and type 18 HPV infection, which causes more than 70% of all cases of CC. The vaccines are injected in 3- or 2-times regimen. In recent years, HPV vaccines have entered national vaccination calendars in many countries. By mid-2013, 45 countries, including Ukraine, had introduced HPV vaccines [2]. HPV vaccination is recommended for all adolescent girls aged 12-14 years. Early vaccination (before sexual activity) is the most effective. However, even at a later age, the vaccine is undoubtedly beneficial. Vaccination has been shown to be effective in preventing cervical pre-tumor and tumor diseases in a number of studies in different countries. The analysis of the cost and effectiveness of HPV vaccination as a method of prevention of CC by Chinese researchers showed that vaccination with the cost of one girl less than US \$50 is undoubtedly beneficial and effective. In comparison with the use of a single CC screening in adult women, the addition of HPV vaccine as a pre-adolescent can reduce the incidence of CC in the population by 44%. American researchers have evaluated the effectiveness of vaccination in the lowest income group of women. The results showed that the delectability of various cytological changes and pathologies was significantly lower among those vaccinated compared to those non-vaccinated (OR=0.64; 95% CI, 0.57-0.73), while the minimum delectability of cervical disease occurred among those vaccinated with 3 doses or when vaccination was given at an age range of 11-14 years (OR=0.36; 95% CI, 0.160.79) [13].

Tobacco smoking prevention and TS abandonment assistance

The second most important managed risk factor of CC is TS. TS have been found to increase the risk of CC and CIN development, especially if the woman started smoking at a

young age and the intensity of TS was high. Therefore, actions and programs aimed at preventing the onset of TS among schoolchildren and students can also be an effective measure to prevent TS, since the onset of TS at a young age has the most adverse effect on the immature epithelium of the cervix and increases the risk of developing TS many times [3]. Anti-tobacco educational programs and actions are needed both for young people and the general public. Certain legislative and administrative measures are also important and effective: raising the price of tobacco products, banning cigarette sales to minors, banning advertising, banning smoking in public places and workplaces. In order to stop and quit TS for regular smokers, most of whom are tobacco addicts, it is necessary to provide affordable, qualified assistance in quitting TS. Relevant surveys among Ukrainian adult smokers show that about 60% of smokers are willing to quit TS. However, among those who try to quit TS on their own, only 1-5% manages to finally get rid of TS. The overwhelming majority of smokers do not manage to overcome their own tobacco dependence. Primary care physicians, including gynecologists at antenatal clinics, should have available methods to motivate them to quit TS and qualified assistance in quitting TS [3].

One of the most effective methods to prevent CC, primarily mortality from CC, is to conduct population-based targeted screening for early detection of people with preclinical stages of cancer or with background and pre-tumor diseases in order to timely treat and eliminate them [2]. For many decades, a fairly effective test for early detection of tumor and pre-tumor changes in the cervix has been widely used for cervical smears in the Papanicolaou cervical canal (Rahr test). Screening programs using the Papanicolaou Smear Test have significantly reduced morbidity and mortality from cervical smears in several high-income countries. In low-income countries, a cheaper, more affordable but fairly effective method of visual inspection with acetic acid is now offered for the screening of CC. Once a direct causal link has been established between HPV infection and the development of CC, it has been suggested that cytological screening be supplemented or even replaced by HPV testing. It has been suggested that HPV testing is even more effective than the cervical neoplasia radar test. Methods have been developed to serologically test and detect HPV DNA for screening precancerous lesions and CC. The correct application of precancerous and CC screening methods based on HPV infection detection and HPV vaccination has been found to reduce the incidence of CC and other tumors etiologically related to the virus. Countries with high morbidity and limited resources can benefit most from relatively inexpensive HPV screening at five-year intervals in order to reduce the incidence of CC. The English authors of more than 20 years of HPV screening for all women aged 25-64 estimated that 23.9% (95% CI: 19.3-27.6%) of clinical cases of CC were prevented by this screening. An optimal preventive screening strategy is proposed for both vaccinated and

non-vaccinated women. All women aged 25-69 years are screened for HPV with HPV genotyping 16 and 18 times every 5 years and a cytological study every 1-2 years. This screening option has been found to be the most effective and most cost-effective.

Conclusion

The key approach to reducing cancer is to prevent the disease rather than treat it. This provision is perhaps the most justified and relevant for CC. With regard to this form of cancer, the etiological mechanisms and risk factors have been well studied and effective measures and technologies to prevent this form of cancer have been developed. However, the cost, effectiveness, and accessibility of these technologies to specific countries, regions, and populations should be considered when introducing them into practical health care. With these criteria in mind, each region should develop its own optimal prevention program for the CC. In particular, vaccines against certain HPV genotypes can be selected, and different intervals can be set for screening of both cytological and HPV. It is important to emphasize that a key position of CC prevention programs is information and education measures aimed at increasing public knowledge about the causes and possibilities of CC prevention. Only with sufficient public awareness and preparedness can the proposed prevention methods reach about 70% of the targeted population. Only with such outreach will prevention technologies be effective enough.

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