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Current knowledge of cervical cancer: pathogenesis, prevention, and treatment. Part I

Rak szyjki macicy: patogeneza, zapobieganie i leczenie. Część I

Cervical cancer is a preventable disease resulting from infection with high-risk types of sexually transmitted human papillomaviruses (HPVs). It is estimated that 6 million new infections HPV occur each year [9]. Public knowledge of HPVs and their link to cervical cancer is limited. The cervix (Fig. 1) is the lower part of the womb, that protrudes into the vagina. Cervical cancer (Fig. 2) is the second most common cancer after breast cancer among women, and the second most common cause of women's cancer deaths. Worldwide, an estimated 466 000 women are diagnosed with cervical cancer each year, and around a quarter of a million die from the disease [5]. The peak incidence of cervical cancer worldwide is in women aged 35 and older. Early detection is vital in reducing the mortality rate and in preserving fertility in women of childbearing age [3]. About 40 % of cervical cancer is diagnosed in women of childbearing age [4, 13].

HPV INFECTION IN CERVICAL CANCER

Cervical cancer is a sexually transmitted disease caused by several types of a virus called Human Papilloma Viruses (HPV) [1, 6]. Most women's bodies are able to fight HPV infection, but sometimes the virus leads to cancer. It is usually preceded by precancerous changes in the cells on the surface of the cervix. Cervical cancer usually may present in one of two ways. Sometimes it is detected in its microscopic form after treatment for dysplasia (lesion which showed changes less severe than carcinoma-in-situ). Otherwise, it usually presents with abnormal vaginal bleeding, bleeding after an intercourse, or discharge. Cervical cancer is usually a slow-growing cancer that may not have symptoms but can be found with regular Pap tests (a procedure in which cells are scraped from the cervix and looked at under a microscope). Pre-cancer changes occur gradually, often over a period of more than 10 years and can lead to cancer if left untreated. By getting regular Pap.tests and pelvic exams we can find and treat changing cells before they turn into cancer. Figures 1 and 2 are examples of histological specimens. Figure 1 is a normal cervix and Figure 2 is a cancerous cervix.

Studies of cervical cancer suggest a direct causal relationship with sexual activity and HPV infection developing. HPV types associated with genital infections are transmitted sexually, primarily through skin-to-skin contact during sexual activity. HPV can also be transmitted through oral sex. Genital HPVs are the commonest sexually transmitted viral infection. The chance of getting HPV rises with certain risk factors: number of lifetime sexual partners (risk increases with more partners), early onset of sexual activity (young age women 20 to 24 are most likely to be infected, but they usually clear the HPV infection with no problems), women who are sexually active with men who

have other partners at the same time. Many women unknowingly carry HPV and the virus naturally regresses on its own over time.Progression to invasive carcinoma depends upon the action of external factors such as hormones (contraceptive pills), chromosomal aberration, carcinogens (such as cigarettes) and immunosupression as well as the type of HPV virus present [14]. HPV is a DNA virus which can cause high-grade cervical lesions. Following infection HPV may incubate for 1 to 8 months before active growth begins. The phase of active growth usually lasts between 3 to 6 months before an immune response is mounted. The immune response can take up to 6 months to contain the virus and a further 9 months before the virus goes into remission. Depending on a number of factors the host may maintain a sustained clinical remission or develop persistent or recurrent disease.

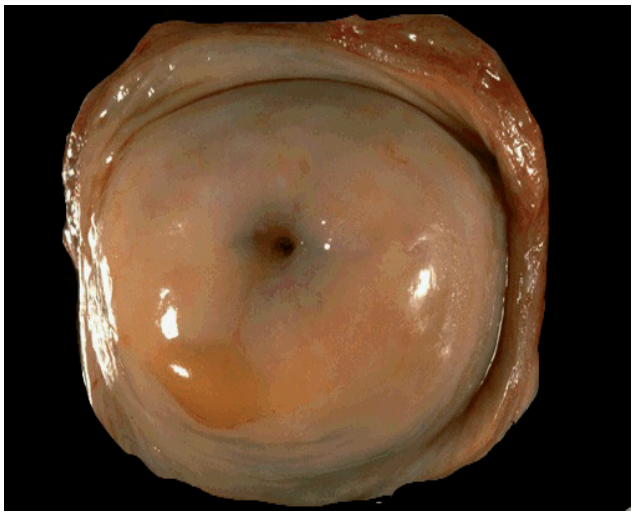

Fig. 1. Normal cervix with a smooth, glistening mucosal surface. There is a small rim of vaginal cuff from this hysterectomy specimen. The cervical os is small and round, typical of a nulliparous woman. The os will have a fish-mouth shape after one or more pregnancies

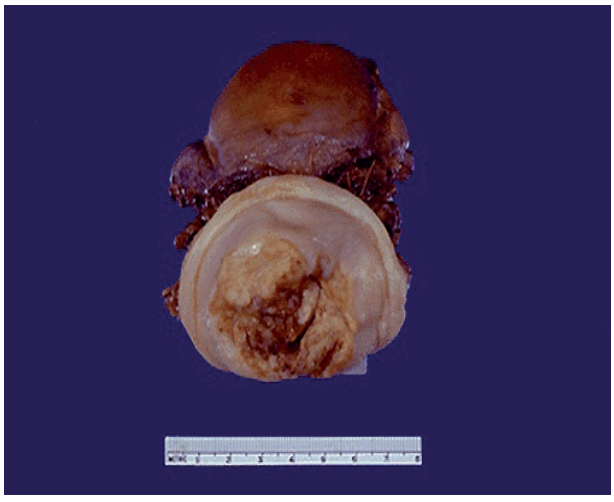

Fig. 2. The gross appearance of a cervical squamous cell carcinoma that is still limited to the cervix (stage I). The tumor is a fungating red to tan to yellow mass

LOW-RISK TYPES OF HPV

There are more than 100 different types of HPV. About 30 types affect the genital tract. Some types are highly oncogenic, others have only small oncogenic potential. Types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 cause genital warts (candyloma acuminatum), approximately 90% of genital warts are caused by HPV types 6 and 11 [10].

HPV only produces visible warts in around 30% of people, leaving 70% of people with HPV who have no signs of the infection [7]. It is extremely common with over 80% of women having contracted it at some time in their life [1]. Most women do not develop cancer and the development of cervical cancer involves a series of genetic and immunological processes that are not fully understood. In the majority of cases, the immune system fights off this infection, but if the infection persists or if a woman is re-infected with any of high risk HPV types there is a higher risk of developing changes in cervical cells and that can lead to cervical cancer.

HIGH RISK TYPES OF HPV

More recently human papilloma viruses (HPV) have emerged as prime suspects since they can be detected in over 90.7 % of CIN III and cervical cancer [12] and they possess transforming viral oncogenes (E6 and E7). HPV are DNA viruses with an icosahedral outer structure is composed of 72 capsomeres. HPVs are present in the animal as well as the human species. There are approximately 14 high-risk types of HPV that cause invasive cervical cancer, types 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82.

HPV types 16, 18, and 31 are the most commonly associated with cervical cancer, and are generally known to cause about 75% of cervical cancer [7], genotypes 16 and 18 are present in over 70% of cases of cervical cancer worldwide [12, 14]. Recently, less prevalent oncogenic HPV genotypes (31, 33, 45, 52, 58, 59) have also been found to be strongly associated with cervical cancer [2]. High risk HPV16, 18, 31, 33, 45, 52 can usually be found in moderate and severe dyskaryosis CIN II/III, invasive carcinoma, AIS (adenocarcinoma in-situ), endocervical adenocarcinoma. Differences are also detected in the physical status of HPV different grades of cervical dysplasia. Low risk HPV 6, 11 are associated with mild dyskaryosis CIN I. Low risk types are maintained as extra-chromosal circular DNA fragments in CIN I lesions while the genomes of HPV high risk are found integrated into the human DNA strands in CIN III lesions and cervical carcinomas. HPV integration appears to be a critical event in the progression to cervical cancer as HPV oncogenes E6 and E7 are conserved intact and show evidence of persistent and increased expression in carcinomas. The main mechanism of action of E6 and E7 from HPV high risk types is rapid inactivation of the host cell's oncosuppressor proteins p53 and Rb. This inactivation does not happen with low risk HPV types [11]. With the improvement of methods to detect HPV at the molecular level there is increasing evidence of the presence of HPV in CIN lesions. The detection of multiple infections has also increased, probably because of the higher sensitivity of the techniques that are currently used. CIN (cervical intraepithelial neoplasia) describes pre-cancer changes of the cervix.

The cellular changes in HPV infections include: multinucleation with large nuclei which may be hyperchromatic, wrinkled, loss of nuclear detail. Characteristic is a paranuclear "halo" with hard edges, as if "punched out" (koilocytosis), condensed peripheral cytoplasm and dyskeratosis (abnormal keratinisation,normal cervical epithelium is non-keratinising). Cellular changes of HPV can exist alone or with dyskaryosis (Fig. 3).

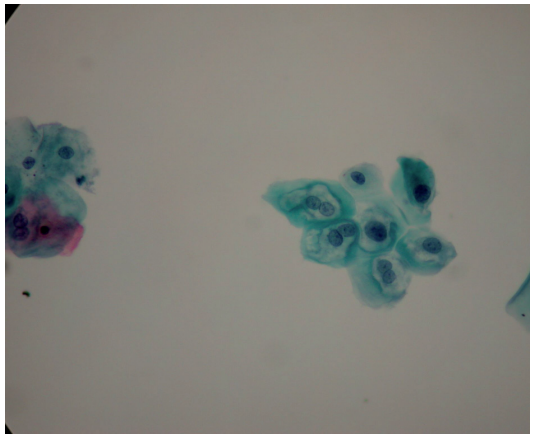

Fig. 3. Koilocytosis

CONCLUSIONS

Human papilloma virus (HPV) is a public health problem as a sexually transmitted disease and as a critical factor in the pathogenesis of various cancers. There is no treatment for the HPV virus, but an immune system can usually fight off HPV naturally. The mean duration of carriage is 4 months for low-risk oncogenic types and 8 months for high-risk oncogenic types, with HPV-16 carriage being even longer [8, 12] There are treatments for the diseases that HPV can cause. Visible genital warts can be removed. Cervical cancer is most treatable when it is early diagnosed and treated. There are new forms of surgery, radiation therapy, and chemotherapy available for patients [2].

Two major pharmaceutical companies have now developed vaccines against specific HPV types. Gardasil, a Merck & Co. vaccine is effective against HPV types 6, 11, 16 and 18 and Cervarix, which is effective against HPV types 16 and 18. Early studies suggest that the vaccine may be almost 100% effective for the prevention of types 16 and 18 CIN when administered before becoming sexually active [4].

To date the most common method of prevention of cervical cancer is regular cervical screening (Paptest). HPV vaccination gives very good effect as well. Also, life style factors are contributing (early onset of sexual activity, early age of first pregnancy, multiple sexual partners and "high risk partners"). Treatment of pre-cancer changes and early stages of cervical cancer can save a woman's life.

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SUMMARY

Cervical cancer is the second most common cancer after breast cancer among women. Worldwide, an estimated 466 000 women are diagnosed with cervical cancer each year, and around a quarter of a million die from the disease. Cervical cancer is a disease resulting from infection with high-risk types of human papillomaviruses (HPV). It is a sexually transmitted disease, often slow-growing with no symptoms until the later stages. Nowadays regular cervical screening is commonly used to prevent disease development (almost 100% effective for the prevention of types 16 and 18). HPV vaccination gives very good effect as well.

STRESZCZENIE

Nowotwór szyjki macicy jest drugim najczęściej występującym nowotworem po nowotworze piersi wśród kobiet. Szacuje się, że 466 tysięcy kobiet na świecie jest diagnozowanych każdego roku na ten typ nowotworu i około ćwierć miliona umiera z powodu tej choroby. Do rozwoju raka szyjki macicy dochodzi w wyniku infekcji wirusem brodawczaka ludzkiego (HPV), typami wysokiego ryzyka. Jest to choroba przenoszona drogą płciową, rozwijająca się powoli, często bezobjawowo aż do późniejszej fazy choroby. Obecnie regularne badanie cytologiczne (Pap.test) to najbardziej popularna forma profilaktyki. Także szczepienie HPV daje bardzo dobre rezultaty (prawie 100% odporność na typy 16 i 18).