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Prevention of cervical cancer

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SUMMARY: **Prevention of cervical cancer.**

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The presence of high-risk HPV subtypes is associated with a substantial risk of cancer (95% of cases). This link is strongest for certain HPV types, particularly types 16, 18, 31 and 45.

Other factors, such as smoking, nutrition, coexisting sexually transmitted diseases and genetics, may play a role in a person's susceptibility to HPV subtypes.

Most infections must either remain permanently latent or only transiently produce cytologic changes missed by infrequent screening. Other women will develop HPV-associated cervical disease, detectable by ***cytologic changes diagnostic*** *of HPV infection.*

Women persistently positive for high-risk HPV types require further immediate evaluation by colposcopy. So HPV-testing could be used to determine which women would be best managed by immediate ***colposcopy*** *(HPV positive) and which by cytologic follow-up (HPV negative).*

RIASSUNTO: **Prevenzione del cervicocarcinoma.**

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Il cancro della cervice uterina è stato associato alla presenza di un'infezione da HPV con genotipo ad alto rischio nel 95% dei casi. Questa associazione riguardava soprattutto i genotipi 16, 18, 31 e 45.

Altri fattori, quali il fumo, l'alimentazione, la presenza di altre malattie sessualmente trasmesse e i fattori genetici, giocano un ruolo importante in pazienti suscettibili di infezione da HPV.

Alcune volte l'infezione può rimanere permanentemente in forma latente o solo transitoriamente produrre delle alterazioni citologiche che possono sfuggire ai controlli di screening.

In altri casi l'infezione da HPV può evolvere verso la patologia cervicale, producendo alterazioni citologiche diagnosticabili.

Donne risultate positive al test per la ricerca di HPV ad alto rischio sono inviate immediatamente ad un controllo colposcopico.

Il test per la ricerca dell'HPV può essere utile per selezionare quelle donne che hanno bisogno di una immediata valutazione colposcopica (HPV positive) da quelle che possono essere controllate mediante un follow-up citologico (HPV negative).

KEY WORDS: HPV-DNA testing - Colposcopy - Cytology.
Test per HPV-DNA - Colposcopia - Citologia.

Much evidence suggests a causal link between HPV infection and cervical neoplasia. The HPV subtypes are divided into three categories according to the risk of oncogenesis *(high-risk, moderate-risk and low-risk types)*. The presence of high-risk HPV subtypes is associated with a substantial risk of cancer (95% of cases). This link is strongest for certain HPV types, particularly types 16, 18, 31 and 45.

The viral genome usually exists in an episomal (circular) configuration that can be divided into three regions, which are known as upstream regulatory region (URR), early region (E), and late region (L1 and L2). Regions E6 and E7 are crucial for the process of oncogenesis as they produce the proteins that are necessary for the transformation of a cell. The integration of HPV into the host cellular DNA appears to be the final step in the transformation of the host cell to an immortalised cancer cell capable of invasion. Once this integration has occurred, the expression of HPV E6 and E7 protein markedly reduces the ability of p53 to destroy the cell (Fig. 1).

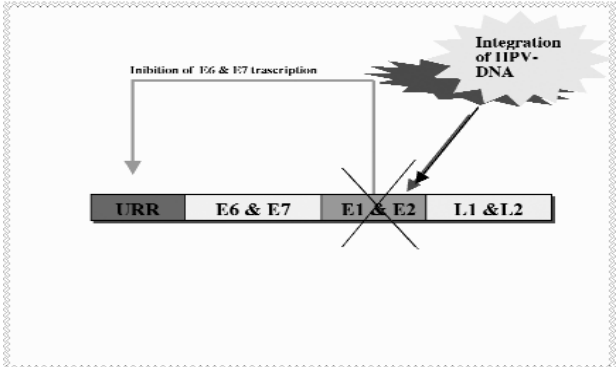

Fig.1 - Integration of HPV into the host cellular DNA.

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Such inhibition may render the cells sensitive to random events that lead to the accumulation of a genetic damage associated with cancerogenesis.

Other factors, such as smoking, nutrition, coexisting sexually transmitted diseases and genetics, may play an important role in a person's sensitivity to HPV subtypes. Genital HPV types are often detected in a normal anogenital mucosa by highly sensitive tests such as polymerase chain reaction (**PCR)** and **Hybrid Capture II**, fulfilling the criteria of " latent" HPV infection, and latent HPV may be found in a normal epithelium adjacent to expressed disease. Latency is an extremely variable period but it is estimated on average from one to eight months. It is not clear whether clearance can occur by immune recognition at this stage or whether immune recognition requires the increased viral numbers of a productive infection to be stimulated. If this is the case, most individuals have such a transient expression that lesions are not detected.

Most infections must either remain permanently latent or only transiently produce cytologic changes which are usually not detected because of infrequent screening. Other women may develop HPV-associated cervical disease, detectable by **cytologic changes diagnostic** of HPV infection, including koilocytotic atypia, or shed cells that have only some, but not all, of the features of an HPV infection (e.g., atypical squamous cells of undeterminated significance or ASCUS) (1, 2). Approximately 60% of women with only minor atypia or SIL low grade have lesions that will spontaneously regress in a period of ten years and another 20-30% will not change. Those 10% who develop high-grade SIL during the follow-up remain persistently HPV DNA positive.

The relative risk (RR) of the progression of the disease from low grade SIL to carcinoma in situ during a period of 24 months is 1.00 (95% CI), while the relative risk of the progression from high-grade SIL to carcinoma in situ is 22,65 (95% CI). After 24 months the relative risk of progression disease from HSIL to carcinoma in situ is reduced to 4.15 (95% CI).

An accurate and early recognition of abnormal cytologic changes reduces the incidence of cervical cancer. In a routine screening interval of 10 years the incidence of cervical cancer was 20%. One or three normal annual Pap smears are documented, the interval for continued monitoring by screening Pap smears may be lengthened at the discretion of the physician and the patients.

Persistent or recurrent ASCUS is a particularly problematic management issue. The addition of a Hybrid Capture®II HPV test to cytology in the follow-up of women, who resulted negative after colposcopy, with "chronic" ASCUS Pap smears may be helpful. Those women who are persistently (on two HPV tests) HPV negative may be asked to undergo cytologic exams every six months, provided that the Pap remains no more abnormal than ASCUS. The high negative predictive value of a single Hybrid Capture®II test for CIN 2-3 and cancer is highly promising and two negative tests should reduce the theoretical false negative rate to a value ranging from 0.49 to 1%. In contrast, women persistently positive for high-risk HPV types need a further immediate evaluation by colposcopy. Therefore, HPV-testing could be used to determine which women would be best managed by immediate **colposcopy** (HPV positive) and which by cytologic follow-up (HPV negative). Estrogen-deficient women may have ASCUS due to the effects of estrogen loss on the mucosa of the lower genital tract. Therefore, before embarking on an extensive work-up on peri or postmenopausal women with ASCUS, the administration of a vaginal *estrogen cream* before undergoing another Pap or colposcopy is appropriate.

The false-negative rate of screening Pap smears in our population ranges from 20 to 30 percent. Further procedures have been developed to address the false negative problem of cytology reports and find women with, or at risk of, cervical carcinoma. New laboratory tests have been developed for primary and secondary screening for cervical cancer and its precursors. The tests are the following: 1) Thin-layer liquid-based cytology (**ThinPrep Pap test**); 2) computer-assisted automated cytology (**AutoPap**). The new strategies of screening include also **cervicography**, a visual examination which involves photography of the cervix following acetic acid wash and analysis of the resulting image under set conditions by experts in colposcopy. A new visual screening procedure, **speculoscopy**, has been recently developed and reported to be a further tool in detecting neoplastic cervical lesions, including the ones that could not be detected through Pap smear. Speculoscopy utilises chemiluminescence and low power magnification (4-6x) to detect the presence or absence of aceto-whitened areas after applying 5% acetic acid on the cervix. This technique seems to allow the collection of diagnostic information, which is similar to the one obtained by colposcopy, but at a lower cost.

For low-grade cervical HPV changes (CIN 1, mild dysplasia) no treatment/observation only:

- Because both genital warts and low-grade cervical dysplasia (CIN1) often go away without treatment, many clinicians either do not treat CIN 1 or they give the patient the option not to treat it. It is estimated that 50-70% of these lesions may spontaneously resolve without treatment. Non-treatment follow-up

usually consists of Paps every 6 months, with or without an occasional colposcopy.

LEEP (Loop electrosurgical excision procedure) has now become the primary treatment modality for lesions extending into the canal and for high-grade (CIN 3) lesions. LEEP uses a thin wire loop through which an electrical current passes and turns the loop into a very effective cutting tool (3). One of the primary advantages of LEEP is that the clinician can see the lesion while it is being treated (excised) and it provides a tissue sample which can be evaluated by a pathologist to be sure that the entire lesion is removed and treated adequately. The relatively low cost of LEEP and the possibility to use this procedure in the office has eliminated the need to do hospital-based cervical conizations in all but a minority of procedures.

Although LEEP is largely utilised in the treatment of large lesions, in this area **laser** is till regarded as the best procedure, especially for those lesions extending towards the cervical-vaginal margin. However, laser is often not available and has a high cost, thus, LEEP has virtually replaced laser even for extremely large lesions. Laser is comparatively very costly because it requires expensive equipment and high maintenance. Additionally, laser requires more training and skills than the other two procedures and implies more serious safety issues (eye injuries and inadvertent burns). Higher cost and the potential for easily removing an excessive amount of the cervix are its main disadvantages.

Cold cone is a procedure in which the clinician removes the portion of the cervix with abnormal cells by cutting the area through a scalpel (a surgical knife). Since the patient usually requires a general anaesthetic (to be put-asleep) (3), this is usually done in an outpatient hospital operating room. Only a few situations require a cold cone. These would include diseases too far up the canal to be ideally removed by LEEP and glandular diseases which may be present in the canal.

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