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PAPILLOMA VIRUSES AND HUMAN CANCERS

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The oncogenes E6/E7 of high risk papillomaviruses are decisive for the proliferative and malignant phenotype of HPV-linked cancers, specifically of cancer of the cervix. In non-malignant cells intracellular and intercellular signals suppress these oncogenes at the transcriptional level. The available data permit the delineation of a functional model of interactive events controlling E6/E7 transcription. Modifications of host cell genes engaged in this control will interrupt this regulatory pathway and result in increased E6/E7 gene expression and, as a consequence, in stimulation of cell proliferation.

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BREAST CANCER MASS SCREENING

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The aim of breast screening is to decrease the mortality of breast cancer by detecting tumors before they metastasize. Since small tumours give rise to fewer distant metastases than large ones, it is logical to diagnose cancers as small as possible. Modern mammography reliably detects cancers of 5-10 mm diameter and has proved to be an efficient screening tool with a sensitivity and specificity better than 95 % and a positive predictive value of 50 % when the incidence of cancer is high. However, it rapidly decreases when the incidence is low, as for example among young women.

When an invitation for mass screening is sent out, the proportion of attenders varies from 60 to 90 per cent. Experience show that non attenders are at a higher risk to die from breast cancers than those who come for screening. Data from one screening trial demonstrate that about 8 - 10 per cent of all breast cancers are stopped in their progression towards metastatic spread.

Screening increases the number of cancer cases, probably due to the detection of clinically "occult" cases. These very small cancers are highly differentiated, have a very low mortality and are probably overtreated with today's methods.

A recent overview of five Swedish randomised studies reveals a significant 24 % risk reduction of breast cancer mortality (95 % conf. limits 13-14 %) among screened women. The effect is clinically insignificant in women 40-49 years but highly significant among those 50-69 years. It is of the same magnitude as that of adjuvant chemotherapy in node positive premenopausal women. However, this reduction hardly influences overall mortality of women since breast cancer accounts for not more than 6 % of all female deaths.

Mass screening for breast cancer should be evaluated from different points of view. The rare individual whose life is saved benefits enormously. The clinician gets more patients diagnose and treat and he probably overtreats some small breast cancers. Breast cancer treatment, even breast conservation, is associated with a certain psychic morbidity and methods have to be devised to reduced this. The health politician experiences increased costs not only for the screening procedure itself but also for the treatment and follow up of more breast cancer cases and must decide how to set priorities for the best use of available resources. Thus, breast mass screening saves the life of women but also creates difficult ethical problems which must now be dealt with by the general public, by doctors and by politicians.

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CELLULAR IMMUNITY AND CANCER

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Paul Ehrlich, at 1909 was already aware of the importance of an intact immune system as a requisite for host resistance against tumor growth. Foley was the first to demonstrate the presence of tumor antigens in mice cells undergoing malignant transformation by the influence of chemical carcinogens. A remarkable feature of chemically induced tumors is that each tumor expresses a different antigen and consequently elicits immunity to itself but not to any other tumor. Similar antigens have been found in virus induced mice tumors which express specific antigens corresponding to viral components. Since spontaneous tumors were seldom found to be capable of inducing immune response, the concept of immune surveillance of cancer was discredited and considered a laboratory artifact. Nevertheless, in the last 15 years it was demonstrated that spontaneous tumors also express weak transplantation antigens that are potential target for immune rejection by the host. Today, it is known that at least two different sets of T cells may participate in mounting an immune response against a tumor. T helper cells (CD4) recognize exogenously derived tumor antigens processed by antigen presenting cells (APCs) to the level of peptide fragments. The complex of these peptide fragments of the antigen associated to MHC class II is displayed in the cell surface and recognized by CD4 T-cells. In addition, Cytotoxic T-lymphocytes (CTL), denoted as CD8, specifically recognize peptides derived from the processing of tumor antigens by APCs in association with class I of MHC complex. The disclosure of T-cell receptor structure has greatly contributed to the understanding of T-cell participation in tumor antigen recognition. This revived version of the immune surveillance hypothesis may explain the increased incidence of cancer in pathological conditions associated with primary or secondary immune deficiency. These observations led obviously to the search of non specific or specific immune therapy against tumors. BCG vaccine in transitional cell carcinoma and levamisol as an adduct to 5-FU in colon cancer are fair examples within the first category. In addition, a synthetic thymic hormone developed in our laboratory (THF-γ2) manifests a considerable antitumor effect in experimental models when given in combination with chemotherapy. AS101 ammonium trichloro (dioxyethylene-O-O') tellurate is another interesting immune modulator developed in Israel.

The measurement of the interaction of T-lymphocytes and tumor antigens may also be useful for early diagnosis of cancer. The Cellscan, an instrument developed in Israel and presently under intensive trial, measures structural changes occurring in a group of lymphocytes upon stimulation with a putative tumor antigen recognized by them .