SPECIAL ARTICLE

Viral Carcinogenesis of the Cervix

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Since the initial report in 1977 by Meisels et al[1] linking pre-invasive squamous lesions of the cervix with an infection by the Human Papillomavirus (HPV), there has been a rapid expansion of knowledge in the field of viral carcinogenesis of the cervix. Much of the increased knowledge was only made possible by concomitant developments in recombinant DNA technology.

The purpose of this review is to summarize current concepts of viral carcinogenesis of the cervix. Secondly, a major purpose is to present implications for cervical screeening and management based on these concepts.

Machanism of Viral Carcinogenesis

It is now widely accepted that an infection of the cervix by an oncogenic strain of HPV is necessary to cause oncogenic transformation[2-4]. More than 60 strains of HPV have now been identified but only about 20 affect the lower female genital tract. Of these 20 strains, only some are associated with cervical carcinoma, the common ones being HPV 16, 18, 31, 33 and 35. The common non-oncogenic strains are HPV 6 and 11. The fundamental difference between oncogenic and non-oncogenic HPV strains is the ability of the former to integrate part of its genome into the genome of the host epithelial reserve cell. That part integrated is constant for each of the oncogenic strains and includes the E6 and E7 genes along with their upstream regulatory region (URR) which controls their activity (i.e. transcription of viral DNA)[5,6].

Only very recently has it been discovered how this integration of the viral genes E6 and E7 effects malignant transformation. Within the human genome there are probably numerous "anti-oncogenes" whose role is to control normal cell proliferation and differentiation. Two such genes include the RB and p53 genes. (The RB or retinoblastoma gene was so named because it was previously found that a defect or mutation was associated with the development of retinoblastoma). These "anti-oncogenes" each produce a protein whose role is to control normal cell proliferation and differentiation. However, the activated E6 and E7 genes each produce a protein product which preciptates and inactivates

the protein product of the p53 and RB genes, respectively[7,8]. As a consequence, control over cell proliferation and differentiation is lost.

Thus, cervical carcinogenesis begins with the integration of viral DNA into the cervical epithelial reserve cell. From that point on, there is a progressive loss of control of cell proliferation and differentiation with each stepwise loss being inherited by the daughter cells. Ultimately, an autonomous clone of cells emerges with the capacity to invade and metastasize.

Pre-invasive Carcinoma

Before a clone of invasive cancer cells emerges, there is a continuum of morphologic changes which reflects the progressive loss of control of cell differentiation, or pre-invasive carcinoma. The older terminology of *Dysplasia/Carcinoma in situ* divided that continuum into four groups as shown in Figure 1A. In that terminology malignant transformation was believed to occur between severe dysplasia and cacinoma in situ.

The term "Cervical Intraepithelial Neoplasia" (CIN) was introduced by Richart[9] in 1967 to describe the same continuum of pre-invasive histologic and cytologic changes of the cervix associated with SCC. These changes were arbitrarily divided into three groups with CIN III including both severe dysplasia and carcinoma in situ (CIS) (Figure 1B). This terminology rapidly replaced the older dysplasia used in many centres. Its fundamental concept that all degrees of CIN are neoplastic has been subsequently validated by recent discoveries of viral oncogenesis : malignant trans-

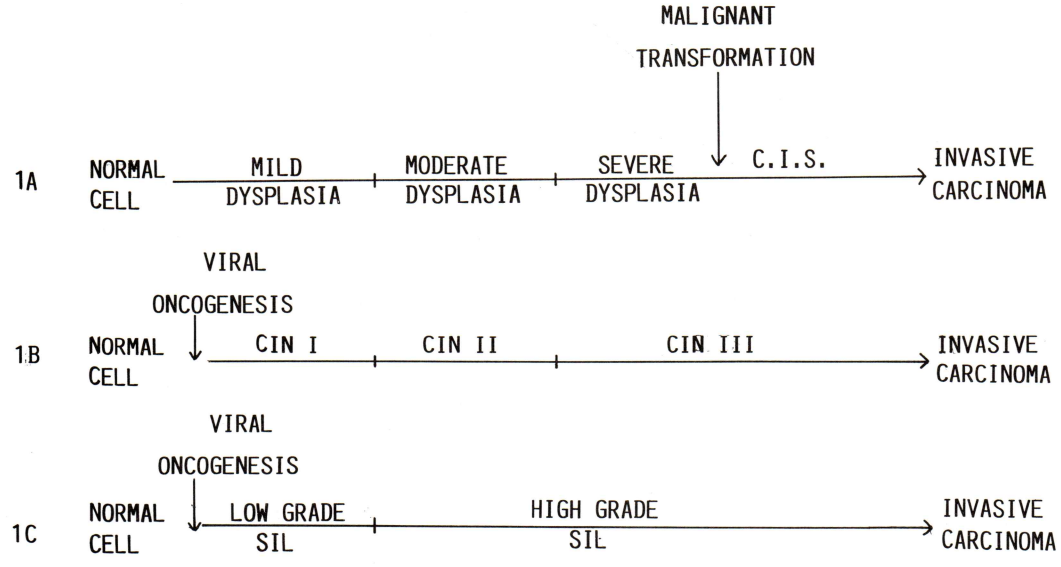

Fig.1 Terminology used to describe pre-invasive cervical SCC.

formation occurs with integration of viral DNA before any morphologic changes are apparent.

However, there is a high diagnostic error rate associated with CIN I. A variety of artefacts all produce slight nuclear changes which are indistinguishable from true CIN I on a Pap smear. These artefacts include infections (e.g. Candida, Trichomonas, various bacteria), chronic irritation (from the string of an intra-uterine contraceptive device), prior irradiation, etc.. Also, an infection by a non-oncogenic HPV strain commonly results in slight nuclear changes reported as CIN I. But, none of these false positive cases of CIN I has the capacity to progress to invasive disease.

In recognition of the high diagnostic error rate associated with CIN I, and in an attempt to further standardize the terminology, the "Bethesda System"[10] has recently introduced the term "Squamous Intraepithelial Lesion" (SIL). The same continuum of morphologic changes would be divided into only two categories: low grade SIL corresponding to CIN I, and high grade SIL corresponding to CIN II and III (Figure IC). (For a review of the controversies surrounding the Bethesda System, see reference 11).

Implications for Cervical Screening and Management

The basic principle of management for a woman whose Pap smear is reported to show any degree of CIN has been to refer that woman for colposcopy. However, the high diagnostic error rate associated with CIN I, the epidemic of cervical HPV infections, and the need to contain health care costs have all forced a re-assessment of that approach. The Third Canadian Task Force on Cervical Cancer Screening Programs is expected to soon recommend[12] that women whose Pap smears are reported as CIN I should have repeat smears every six months for up to 24 months. Only those women whose smears progress to CIN II or III, or those whose CIN I persists at the end of 24 months should be referred for colposcopy.

Realizing that there is a lag period of several years between viral integration (malignant transformation) and the development of invasive disease, the Task Force is also expected to recommend that after two normal satisfactory smears one year apart, women be re-screened only every third year. (For a review of the Task Force's recommendations, see reference 11). This is similar to recent screening recommendations suggested by the American Cancer Society[13].

The Future

Further advances in viral oncogenesis may reasonably be expected in the future to alter our approach to screening and management of cervical SCC. Will a vaccine some day be available to prevent this disease ? Advances in DNA technology, for example, may convert traditional cy-

tology screening into a biochemical test for the detection of integrated E6 or E7 or their protein products.

Further knowledge of the world-wide epidemiology of oncogenic HPV strains is also needed. Are there subtle differences in the behavior of carcinomas derived from various oncogenic HPV strains ? Until the answer to the latter question is clear, modifications to the above screening and management recommendations may be necessary based on local experience considering local resources and expertise[14].

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