Aetiology, pathogenesis, and pathology of cervical neoplasia

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Abstract
Early epidemiological studies of cervical neoplasia suggested a causal relation with sexual activity and human papillomaviruses (HPVs) have emerged as prime suspects as venerally transmitted carcinogens. HPVs fall into two broad camps: low risk types, associated with cervical condyomata and CIN 1; and high risk types (mostly 16 and 18), found in 50–80% of CIN 2 and CIN 3 lesions, and 90% of cancers. This association with cancer is very strong, with odds ratios of >15 (often much higher) in case-control studies that are methodologically sound. An infrequently detected third group of intermediate-risk types HPVs is associated with all grades of CIN and occasionally with cancers. HPVs have also been detected in a wide range of asymptomatic controls, indicating that other events are required for development of neoplasia such as viral persistence and/or altered expression of viral genes, often following integration of the viral genome. This leaves the two major viral oncogenes, E6 and E7, directly coupled to viral enhancers and promoters, allowing their continued expression after integration. High risk HPV E7 proteins bind and inactivate the Rb protein, whereas E6 proteins bind p53 and direct its rapid degradation. A range of putative cofactors has been implicated in progression: HLA type, immunosuppression, sex steroid hormones, and smoking; most of these cofactors appear to influence progression to CIN 3. The natural history includes progression to CIN 3 in 10% of CIN 1 and 20% of CIN 2 cases, whereas at least 12% of CIN 3 cases progress to invasive carcinoma. Cervical glandular intraepithelial neoplasia (CGIN) often coexists with squamous CIN, and the premalignant potential of high grade CGIN is not in doubt, but the natural history of low grade CGIN remains uncertain. A high proportion of CGIN lesions and adenocarcinomas are HPV positive, and HPV18 has been implicated more in glandular than in squamous lesions. A strong clinical case for the application of HPV typing of cells recovered from cervical scrapes can be made; however, a rigorous cost-benefit analysis of introducing HPV typing into the cervical screening programme is required. Prophylactic and therapeutic HPV vaccines are under development. This article reviews the aetiology, pathogenesis, and pathology of cervical neoplasia, emphasising the role of HPVs.

Keywords: human papillomavirus; cervical neoplasia

This review is based on three presentations by the authors to the first National Cervical Screening Conference organised by Marie Curie Cancer Care and held in Oxford, UK in September 1996. It also includes several more recent developments. It is important to emphasise that the cervical screening programme aims to detect women who have an epithelial abnormality that might, if untreated, lead to the development of cervical carcinoma. The screening programme is not designed to detect small or early invasive carcinomas, but no screening system will detect all women at risk and it is inevitable that in a small proportion of smears, evidence of invasive cancer will be found. Cervical smears may also identify non-neoplastic epithelial changes, such as koilocytosis and multinucleation, which are believed to be associated with infection by human papillomavirus (HPV), which is strongly suspected to play an aetiological role in cervical neoplasia. Analysis of the effectiveness of the cervical screening programme and its further development should be based on a clear understanding of the aetiology, pathogenesis, and pathology of cervical neoplasia.

Aetiology of cervical neoplasia
Early epidemiological studies of cervical neoplasia suggested a direct causal relation with sexual activity, measured as multiple sexual partners and early onset of sexual activity.1 A further risk factor was exposure to the “high risk man”, characterised by a history of promiscuous sexual activity and/or sexual exposure to a partner who develops genital neoplasia. Over the past 20 years the search for venerally transmitted carcinogens has included components of semen and various viruses, including Epstein-Barr virus, cytomegalovirus, and herpes simplex II virus (HSV), but without success. The lack of persistent HSV viral DNA, RNA or protein in most neoplastic lesions, and the equivocal findings in prospective studies of HSV in cervical cancers do not support a key aetiological role for HSV in cervical cancer.1 However, HPVs have emerged as prime suspects, being at the scene of the crime carrying the tools to start the job: high risk HPVs are consistently found in over 90% of cervical cancers and they possess transforming viral oncogenes (E6 and E7).
Papillomaviruses
Papillomaviruses are members of the Papova-viridae family with an icosahedral structure composed of 72 capsomers and containing closed, circular, double stranded DNA of approximately 8 kb in length. They are classified by the host species infected and by the degree of DNA sequence homology within specific viral genes. New HPV types must share less than 90% identity within the L1 gene compared to existing types. Seventy seven types of HPV have been cloned and identified to date with more in the pipeline.\textsuperscript{1}

MORPHOLOGICAL EVIDENCE OF HPV INFECTION IN THE LOWER GENITAL TRACT
The most common manifestation of HPV infection is condyloma acuminata, and in the vast majority of cases this is caused by infection by a non-oncogenic form of HPV, most commonly HPV types 6b and 11. Condylomata acuminata are exophytic, papillary lesions composed of long or short fronds of connective tissue covered by an acanthotic squamous epithelium; the lesions may be multiple. In the cervix and vagina, the epithelium covering the condyloma is usually parakeratotic but may be focally orthokeratotic. Characteristic cellular changes, which are limited to the superficial layers of the epithelium, include individual cell keratinisation, multinucleation, and koilocytotic atypia. Koilocytes are characterised by the presence of perinuclear cytoplasmic vacuolation and nuclear enlargement, hyperchromasia, and irregularity. Similar cytological changes can be seen in a flat, non-papillary epithelium, and in such cases the lesion may be apparent only on colposcopic examination when it may be aceto-white, Schiller positive, and have an abnormal vascular pattern. Such lesions can be distinguished from cervical intraepithelial neoplasia (CIN) by the absence of nuclear atypia in the basal layers of the epithelium.

HUMAN PAPILLOMAVIRUS TYPES AND CERVICAL NEOPLASIA
Early studies quickly demonstrated that HPVs detected within the cervix fell into two broad camps: low risk types, such as HPV6b and 11 associated with low grade lesions, including cervical condylomas and CIN 1; and high risk types, mostly HPV16 and 18 found in 50–80% of CIN 2 and CIN 3 lesions, and up to 90% of invasive cervical cancers.\textsuperscript{2–9} Furthermore, polymerase chain reaction (PCR) based assays strongly suggest that HPV infections cause most CIN lesions.\textsuperscript{4} Munoz and Bosch\textsuperscript{1} have recently reviewed the available epidemiological data on the association of HPV and cervical cancer and found that the data fulfil the Bradford Hill criteria of causality; this conclusion was endorsed by an international multidisciplinary group.\textsuperscript{17} The association between cervical cancer and certain HPV types is: (1) very strong, with odds ratios of > 15 (often much higher) in case-control studies that are methodologically sound; (2) consistent in high risk and low risk countries for cervical cancer; (3) specific for high risk HPV types (HPV16 accounts for the most, followed by HPV18); (4) supported by studies that show HPV infection precedes development of CIN 2/3; and (5) biologically plausible with laboratory evidence of the oncogenic potential of high risk type HPV genes (E6 and E7 viral oncogenes).

Many epidemiological studies have consistently shown that over 90% of cervical cancers can be attributed to specific HPV types. The small proportion of cancers apparently negative for HPV may be either false negatives, reflecting failure to detect new HPV types or very low levels of known HPV genomes, or true HPV negative cancers and thus comprise a separate group. There is some evidence that HPV negative cancers are found more often in older women and are associated with a poorer prognosis. Furthermore, early studies suggested a possible different molecular pathway of carcinogenesis with p53 mutation found only in HPV negative tumours (see later).\textsuperscript{19}

HPV GENOME INTEGRATION AND VIRAL ONCOGENE EXPRESSION
Important differences in the physical status of HPV DNA have been demonstrated in cervical neoplasms. Low risk HPV types 6b and 11 are maintained as extrachromosomal, circular DNA episomes in low grade cervical lesions, whereas the genomes of high risk HPV types 16 and 18 are found integrated into the cellular DNA in most human cervical carcinomas and carcinoma derived cell lines.\textsuperscript{15, 20} Although the site of viral DNA integration into the host other events are required for development of neoplasia, such as viral persistence and/or altered expression of viral genes. It is clear that only a small minority of persistent HPV infections progress to cancer.

HPV types have different effects on the CIN–cancer sequence. An approximate measure of the risk of transition from precursor to cancer can be calculated using the ratio of HPV type prevalence in squamous cancers to that in dysplastic squamous intraepithelial lesions (cancer:CIN prevalence ratio). Several studies have shown that HPV18 is associated with a higher cancer:CIN ratio than HPV16,\textsuperscript{11, 12} suggesting that HPV18 confers a more aggressive neoplastic phenotype than HPV16.
that p53 mutations are observed only in HPV negative tumours have not been confirmed by recent studies. Temporal functional abrogation of p53 and Rb by HPV E6 and E7 proteins is important for viral DNA replication in senescent or terminally differentiated (non-cycling) squamous epithelial cells. Following viral DNA integration during carcinogenic progression, E6 and E7 are persistently expressed causing profound loss of function of p53 and Rb proteins.

These HPV mediated effects on p53 and Rb tend to drive cellular movement around the cell cycle as both p53 and Rb are negative growth regulators that control transit from G1/G0 to S phase. p53 also acts as a “guardian of the genome” and is involved in responding to DNA damage by inducing either growth arrest or cell death by apoptosis. Thus, HPV mediated loss of p53 function decreases the cancer cell’s susceptibility to apoptosis, and promotes cellular survival after DNA damage or development of genomic instability, allowing accumulation of genetic changes that may drive further progression to malignancy. HPV's have a third oncogene, E5, which appears to alter signalling from growth factor receptors for epidermal growth factor and platelet derived growth factor. As E5 is often lost or not expressed after viral integration its role in the later stages of cervical carcinogenesis is uncertain, although it may contribute to development of low grade CIN lesions.

**CLINICAL APPLICATION OF HPV RESEARCH**

There is as yet no clinical situation in which knowledge of the presence of HPV infection or indeed the HPV type, determines clinical management. There is now abundant evidence that women harbouring HPV16 in their cervixes are at greater risk of neoplastic progression, and in the presence of negative or mildly abnormal cytology, are more likely also to have a severe histological lesion, such as CIN 3. A strong clinical case for the application of HPV typing of cells recovered from cervical scrapes can be made. There are two possible approaches: first, HPV typing could augment or indeed supplant the initial cervical cytological screen; second, HPV typing could be used for cases with borderline or mildly dyskaryotic cervical smears to identify a subgroup at high risk of progression. However, a rigorous cost-benefit analysis of introducing routine HPV typing into the cervical screening programme has yet to be carried out in the UK; some trials are in progress in the Netherlands. Prophylactic and therapeutic HPV vaccines are under development, with some therapeutic vaccines targeted to induce an immune response against tumour cells that express HPV E7 protein.

**Pathogenesis and pathology of cervical neoplasia**

**COFACTORS AND CERVICAL NEOPLASIA**

Epidemiological studies have thrown up a range of putative cofactors involved in progression: HLA type, immunosuppression, sex steroid hormones (based on associations of cervical cancers with high parity and long term use of the oral contraceptive pill), and
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smoking. Furthermore, most of these cofactors appear to influence progression to CIN 3 (from latent HPV infection or low grade CIN), rather than CIN 3 to cancer. The effects of smoking have been well studied and there is a consistent epidemiological association (odds ratio of about 2) between cigarette smoking and cervical cancer. The carcinogenic constituents of tobacco smoke are strong candidates for co-carcinogenic factors with HPVs in cervical carcinogenesis. Cigarette smokers with mildly abnormal cytology are more likely to have larger and more severe histological lesions. The constituents of tobacco smoke (such as nitrosamines) can be demonstrated in cervical mucus, and increased smoking related DNA adducts have been shown in normal epithelium next to cervical intraepithelial and invasive neoplasia, indicating a direct effect on cervical epithelium at the DNA level.

Cervical expression of cytochrome P450 enzymes, which activate carcinogenic nitrosamines, and glutathione S transferase, which denatures them, may play a role in determining individual susceptibility to tobacco related carcinogens.

ALTERATIONS IN CELLULAR ADHESION

MOLECULES

Integrins are transmembrane glycoproteins important in interactions between epithelial cells and basement membranes. Integrin expression is confined to the basal layer of normal squamous epithelium. However, the patterns of integrin expression in neoplastic cervical epithelium differ from this, with dysplastic cells expressing integrins throughout the full thickness of the epithelium in CIN 3.

Epithelial cadherin (E cadherin) is a cell–cell adhesion molecule that connects epithelial cells via homotypic, calcium dependent interactions. In normal cervix, E cadherin is expressed on the cell membrane of basal and parabasal cells. Cytoplasmic reactivity is present in occasional basal cells only. In CIN, there is increased cytoplasmic reactivity, which is strongly correlated with the grade of the CIN lesion. In squamous carcinomas, reduced membranous and increased cytoplasmic reactivity is seen with worsening differentiation.

CERVICAL INTRAEPITHELIAL NEOPLASIA

The normal cervix is covered on its outer surface by a non-keratinising, stratified squamous epithelium, which is continuous below with the squamous epithelium lining the vagina, and above abuts onto the mucus secreting columnar epithelium lining the endocervical canal and its associated crypts. The junction between the two epithelia normally coincides with the external os but this is not a constant relation. At puberty, in pregnancy (particularly the first one), and in some steroid contraceptive users, changes in the size and shape of the cervix result in the squamocolumnar junction being carried out on to the anatomical ectocervix. This exposes the tissues previously found in the lower endocervical canal to the vagina. This is a physiological process and the exposed tissue forms the “cervical ectopy”.

It is from the epithelium that covers the ectopy that most CINs and invasive carcinoma develop. Under physiological conditions, the columnar epithelium of the ectopy undergoes metaplasia to a stratified squamous epithelium, and it is during this metaplastic process that the epithelium seems to be particularly vulnerable to oncogenic viruses, and perhaps to other factors resulting in the development of an intraepithelial neoplasm rather than a normal epithelium. The intraepithelial neoplasm may be of squamous or columnar cell type.

CIN is recognised by disturbances of cellular maturation and stratification, and by the presence of cytological atypia. It is customarily graded according to the degree of cytoplasmic maturation but, by definition, nuclear atypia must be present at all levels of the epithelium. It affects the surface epithelium and extends down into the underlying crypts. In younger women, CIN lies on the ectocervix where the ectopy has formed, but in older women the tissues that form an ectopy are withdrawn into the endocervical canal, therefore, CIN in older women tends to lie within the endocervical canal where it may be more difficult to sample. CIN initially forms a single area and thus, if the resection margins of tissue removed for its treatment are free from disease, it is likely that the whole of the lesion has been removed.

Histopathological diagnosis of cervical intraepithelial neoplasia

In Europe, CIN is usually divided into three grades, although other schemes are used. The lesions range from a well differentiated intraepithelial neoplasm (CIN 1) to a poorly differentiated intraepithelial neoplasm (CIN 3). CIN 2 occupies an intermediate position. The differentiation of CIN is rarely uniform throughout the whole area, the most poorly differentiated component tending to lie adjacent to the columnar epithelium of the endocervical canal. For a diagnosis of CIN, nuclear abnormalities such as enlargement, pleomorphism, and hyperchromasia must be present at all levels in the epithelium, including the basal layer. Hyperchromasia is not a prerequisite, and in some forms of CIN the nuclei do not stain darkly. The degree of nuclear atypia tends to be greater in CIN 3 than in CIN 1. Normal mitoses vary in number and do not affect the diagnosis, while atypical mitoses may be present in all grades of CIN. In CIN 1, cytoplasmic maturation occurs in the superficial two thirds of the epithelium. In CIN 2 it starts in the middle third of the epithelium, and in CIN 3, cytoplasmic maturation, which is minimal or even absent, occurs only in the most superficial third of the epithelium. Changes usually attributed to the presence of HPV infection, such as koilocytosis and epithelial multinucleation, are often present and are most conspicuous in CIN 1 and 2, and minimal or absent in CIN 3. This may be a reflection of viral integration in the high grade lesions.

Most histopathologists in the UK have not accepted the two tier Bethesda system for
cervical intraepithelial abnormalities, but have chosen to retain the present grading system, together with a recently introduced category of epithelial abnormality to encompass lesions in which a diagnosis of CIN cannot be made with certainty: basal abnormality of uncertain significance. This category may be particularly useful in combating the problem of overdiagnosis of CIN 1, still thought to occur to a considerable extent, because pathologists fail to appreciate that, even in a CIN 1 lesion, the nuclei are abnormal throughout the full thickness of the epithelium and not just in the lower third above which there is cytoplasmic maturation. However, it is possible to distinguish between CIN 1 and HPV infection alone by virtue of the presence of koilocytosis without nuclear atypia.

**Natural history of cervical intraepithelial neoplasia**

Review of the world literature on the natural history of CIN indicates that the approximate likelihood of regression of CIN 1 is 60%, persistence 30%, progression to CIN 3 10%, and progression to invasion 1%. The corresponding approximations for CIN 2 are 40%, 40%, 20%, and 5%, respectively. The likelihood of CIN 3 regressing is 33% and progressing to invasion greater that 12%. Thus, even the higher degrees of atypia may regress in a significant proportion of cases, and although the probability of an atypical epithelium becoming invasive increases with the severity of the atypia, this does not occur in every case.

As 50–60% of the lesions diagnosed as CIN 1 will regress spontaneously, if clinicians intervene at such an early phase of the process it may result in the unnecessary treatment of women who are at little or no risk of developing carcinoma. A balance has to be struck, however, between unnecessary treatment and a failure to eradicate a lesion that has the potential to progress to invasive carcinoma. In general, persistence of CIN 1 is regarded as an indication for eradication. It is also recognised that higher grade lesions of CIN 2 and 3 are more likely to progress to invasive carcinoma and are usually treated without undue delay.

**Invasive potential of CIN 3**

No one doubts the malignant potential of high grade CIN since the debacle at the National Women's Hospital in Auckland, New Zealand in the 1970s, in which many women with persistent abnormal cytology following biopsy of “carcinoma in situ” (as it was called at that time) were treated conservatively. Twenty nine of 131 women (22%) developed invasive cervical cancer (compared to 1.5% of a control group), and eight died.

The main histological features identified in CIN 3 associated with microinvasive carcinoma or predictive of subsequent microinvasion are extensive involvement of surface epithelium and deep endocervical crypts by expansile CIN 3, luminal necrosis, and intraepithelial squamous maturation. Other features more commonly present in CIN 3 associated with microinvasive carcinoma include frequent mitosis and apoptosis, pericytotic concentric fibroplasia, pericytotic inflammatory infiltrates, pronounced cellular pleomorphism, certain nuclear changes (distinct nucleoli and chromatin clearing), and the emergence of streams of darkly staining spindle cells orientated at right angles to the basement membrane. In a prospective study, 83% of cases illustrating the major microinvasive carcinoma associated features revealed evidence of microinvasive carcinoma or frank invasion either on serial sections of the original biopsy or on subsequent biopsy. None of the 64 cases of CIN 3 that lacked these features showed evidence of invasion on serial sections or on follow up over 18 months. When these features are present in a biopsy specimen, serial sections should be performed to exclude the presence of microinvasion, and closer clinical follow up of these patients is appropriate.

**INVASIVE CARCINOMA OF THE CERVIX**

Most invasive carcinomas of the cervix develop from an intraepithelial neoplasm that has formed in the tissues of the cervical ectopy. They tend to lie, therefore, on the ectocervix in younger women and in the endocervical canal in older woman (see above). The tumours may have an exophytic or endophytic pattern of growth, those on the ectocervix being more commonly exophytic and those in the endocervical canal more commonly endophytic. This has clinical importance in that exophytic tumours on the ectocervix are less likely to have extended into the adjacent tissues and organs than endophytic tumours of similar size, and are less likely to have metastasised.

Cervical carcinomas spread locally into the cervical stroma, the paracervical and parametrial tissues, the body of the uterus, the vagina, and, late in the course of the disease, to the bladder and rectum. Lymphatic permeation in the cervical stroma may occur even when the tumour is of low volume, therefore, metastases may be found in the pelvic lymph nodes even when the tumour is small. It is not possible, therefore, to equate “small” with “early” carcinoma.

**MICRONINVASIVE SQUAMOUS CARCINOMA OF THE CERVIX**

It is customary to stage invasive carcinomas of the cervix according to the criteria laid down by FIGO. The FIGO guidelines do not use the term microinvasive carcinoma, but stage 1A, which encompasses lesions that can be diagnosed only on microscopy, and are usually regarded as being synonymous with microinvasive carcinoma. When invasive disease is identified unexpectedly in women who have been regularly screened, the carcinomas often come into this category. Such a finding should not be regarded as a failure of the screening process because such neoplasms carry only a low risk of metastatic disease and can, therefore, usually be treated relatively conservatively.

FIGO has recently modified its classification of microinvasive carcinoma by subdividing stage 1A. Stage 1 (carcinoma strictly confined
The cervical glandular intraepithelial neoplasia (CGIN) is a term used to encompass adenocarcinoma in situ and glandular atypia in the endocervix. CGIN is much less common than CIN but, as with CIN, most CGIN lesions occur in the region of the cervical ectopy. In contrast to CIN, in about 10% of CGIN cases, separate foci may be found higher in the endocervical canal. Both the surface epithelium and the underlying crypts may be affected by the process, and the junction between the atypical columnar epithelium and the normal columnar epithelium is invariably abrupt. In typical CGIN lesions there are no convincing evidence in the literature that capillary-like space involvement is associated with lymph node metastases or an increased incidence of recurrence. Therefore, permeation of endothelial lined spaces is ignored for the purposes of staging.

The term microinvasive carcinoma can be applied to squamous carcinomas, adenocarcinomas, and adenosquamous carcinomas. For microinvasive carcinomas, the curettings do not contain abnormal epithelium. For microinvasive carcinomas invading between 1 and 3 mm, nodal involvement was found in only 5 of 809 (0.6%) patients who had pelvic lymph node dissection, and the vast majority of these cases can be safely treated by conisation alone. For tumours penetrating 3–5 mm (FIGO stage IA2), there appear to be a higher risk of recurrence and nodal metastasis; nodal involvement has been reported in 14 of 214 patients (6.5%).

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disturbances of both crypt architecture and columnar cell differentiation. Crypts become more complex in shape with outpouchings and infolding of the lining, and they come to lie closer together than usual. The glandular epithelium is stratified, there is a reduction in intracytoplasmic mucin, and an increase in nucleo:cytoplasmic ratios. The nuclei are hyperchromatic and pleomorphic to a variable degree. Nucleoli may be large and multiple. Mitoses are frequent and atypical forms may be present. The columnar cells may remain recognisably endocervical, but intestinal metaplasia is not uncommon. The criteria for grading CGIN are not fully established or agreed, therefore, it is suggested that until the grading system is further evaluated, the range of CGIN lesions be termed either high grade CGIN, corresponding to adenocarcinoma in situ, or low grade CGIN for lesser degrees of abnormality. The malignant potential of high grade CGIN (adenocarcinoma in situ) is not in doubt, but the true natural history of low grade CGIN remains uncertain. CGIN often co-exists with squamous CIN and for this reason may sometimes be overlooked. Abnormalities of oncoprotein expression have been demonstrated in CGIN.

The association between CGIN and HPVs is less clear cut than for squamous lesions, but a high proportion of adenocarcinomas are HPV positive using the sensitive polymerase chain reaction technique. Some workers have suggested that HPV type 18 is implicated more in adenocarcinoma than in squamous lesions.

ADENOCARCINOMA OF THE CERVIX

Invasive adenocarcinoma is reported to be increasing in incidence, particularly in young women, and there have been suggestions of a link between cervical adenocarcinoma and the contraceptive pill, particularly with prolonged use. The practical assessment of microinvasive adenocarcinoma of the cervix is much more difficult than its squamous counterpart, because recognition of the point of invasion and therefore its measurement is associated with problems of definition. However, recent work confirms that lesions with a volume of less than 500 mm³ have a negligible risk of local recurrence and therefore its measurement is associated with more advanced cervical neoplasia than HPV 16. It is not in doubt, but the true natural history of low grade CGIN remains uncertain. CGIN often co-exists with squamous CIN and for this reason may sometimes be overlooked. Abnormalities of oncoprotein expression have been demonstrated in CGIN.

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