Colposcopy and cervical intraepithelial neoplasia

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Abstract

Cervical cancer is caused by certain types of Human Papillomavirus (HPV) and is preceded by a long pre-cancerous stage of Cervical Intra-epithelial Neoplasia (CIN). Cervical cancer can be prevented by successful introduction of an HPV immunization programme and screening using HPV testing, cytology and colposcopy. In the last decade and going forward, significant progress has been made in cervical screening methodologies, which are likely to further reduce the disease burden of cervical cancer and morbidity associated with CIN. We now have a better understanding of the natural history of HPV infection and progression of CIN. Three vaccines are currently available and immunization programmes are well established in developed and developing countries. Cytology screening is currently done using liquid based cytology with additional HPV testing for triage and test of cure. This will be replaced in the UK, in the near future, with primary HPV screening. New adjunctive technologies to Colposcopy are now available that improve the sensitivity of Colposcopy and have the potential to reduce the morbidity associated with CIN.

Keywords cervical cancer screening; CIN; colposcopy; HPV

Introduction

Cervical cancer is one of the commonest malignancies affecting young women. In 2012 the International Agency for Research in Cancer (IARC) reported 528,000 new cervical cancer cases together with 266,000 deaths worldwide from cervical cancer. Nearly 85% of the disease burden and the deaths thereof occurred in the developing world. This wide disparity is attributed mostly to the availability and coverage of well-established screening programmes in the developed world. In the UK since the cervical screening programme was introduced in 1988 there has been a marked decrease in cervical cancer incidence from 16.2/100,000 female population to 8.3/100,000 over 20 years. In stark contrast countries like Uganda and Estonia have reported an increase in the incidence of Cervical Cancer.

What is cervical intraepithelial neoplasia (CIN)?

CIN is the precursor of invasive squamous cell cancer of the cervix. It occurs due to the dysplastic growth of squamous cells on the surface of the cervix. Like other intra-epithelial neoplasia, CIN is not malignant and is completely curable. In the majority of cases CIN would either remain stable or regress as the immune system eliminates the HPV virus that causes it.

Aetiology and risk factors

Human Papillomavirus (HPV) is the single biggest risk factor in the development of cervical cancer or pre-cancer (CIN). To date there exists over a 100 HPV types. Of these, HPV types 16 and 18 are responsible for 66% of cervical cancers. HPV types 31, 33, 45, 52 and 58 account for a further 15% of cervical cancers. HPV 16 DNA would be the commonest in squamous carcinomas, while HPV 18 DNA would be commoner in adenocarcinomas.

Other risk factors for CIN exist, however these risks seem to be associated with a higher risk of HPV contraction and persistence rather than being aetiological agents. These risk factors include early onset of sexual activity, multiple partners, sexually transmitted infections such as Herpes Simplex/Chlamydia, smoking, low socio-economic class and HIV.

Natural history of HPV infection and CIN

The process by which HPV induces neoplasia is now better understood. Most cases of cervical HPV infection occur in young adults aged 18–28. The infection in itself is transient and most women (90%) would clear it within 6–14 months. A minority (10%) of women however end up with viral persistence. This is described as a **latent infection**. The virus stays within the basal layer of the epithelium without integrating with the host DNA. In women with a latent infection, cytology and colposcopy will be negative. 10–20% of these latent infections will progress to a productive infection. In a *productive infection* (Figure 1) the virus reaches the superficial and intermediate layers of the epithelium. The viral genome integrates with the host DNA and there is expression of viral E1, E2 and E4 proteins, which causes replication of viral DNA. In the superficial layer of the epithelium there is expression of viral LI and L2 proteins leading to formation of the complete virion particle, which is shed and can infect adjacent cells. A productive infection however, will not lead to cervical cancer in the majority of women. Cytology and on colposcopy these women will generally have features of low grade CIN. In 10% of women with a productive infection and very rarely in women with a latent infection, the viral DNA integrates with the host DNA and causes expression of viral E6 and E7 proteins which leads to the loss of cell cycle control, mitosis and uncontrolled cell proliferation resulting in a *transforming infection* (Figure 1) which can subsequently lead to invasive cervical cancer. On cytology, histology and colposcopy these women will generally have features of high grade CIN.

Classification OF CIN (Table 1)

Traditionally CIN has been graded as CIN 1, 2 and 3 depending on the degree of differentiation of the cervical squamous epithelium. The diagnosis relies on features of nuclear abnormalities, cell stratification and the proportion of the thickness of the undifferentiated epithelium.

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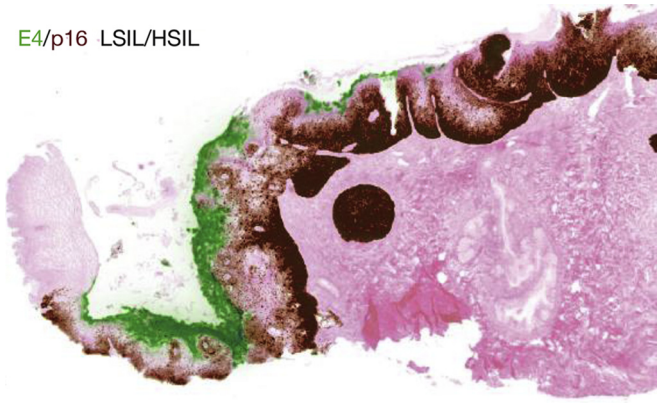

Figure 1 Transforming versus productive infection. Immunohistochemistry staining using p16 (red) and E4 (green). p16 is a surrogate marker of E7 expression. The image demonstrates that as a low-grade lesion transforms into a high-grade lesion (CIN 1 to 3), p16 staining is dramatically increased while E4 staining (associated with a productive infection) diminishes in intensity. (Courtesy of Professor John Doorbar, HPV Lab, University of Cambridge).

However, when providing guidance for patient management, the three-tier grading system is of limited value. Patient management is based on a two-tier grading system of low-grade CIN (CIN1) and high-grade CIN (CIN2 and CIN3) abnormalities.

The WHO histological classification of 2014 has modified the classification of intraepithelial lesions into two grades and currently classifies them into Low Grade CIN which would correspond to CIN1 or LSIL and High Grade CIN corresponding to CIN2, CIN3 or HSIL.

Histological grading using traditional HE staining is complicated by − 1) other conditions such as inflammation and atrophy which mimic changes of CIN and alter the histological interpretation and 2) the high inter-observer variability in grading CIN.

With a clearer understanding of the HPV viral gene expression producing different states of HPV infection (latent infection, productive infection and transforming infection), it is now possible to use biomarkers in differentiating between low grade (productive infection) and high-grade lesions (transforming infection).

Various biomarkers can be used to identify E6 and E7gene expression (p16) as well as cellular proliferation (Ki 67, MCM and E4). Histological staining with these biomarkers has shown to improve the sensitivity in the diagnosis of a transforming infection over traditional HE staining. This would be particularly useful in the medical management of younger women with a histological diagnosis of CIN2 on traditional HE staining. Immunostaining has the potential to differentiate between a productive and transforming infection and thereby help to decide which of these young women need treating.

CIN classification systems

Dysplasia terminology	Original CIN terminology	Modified CIN terminology	The Bethesda system (SIL) terminology (1991)
Normal	Normal	Normal	Within normal limits benign cellular changes (infection or repair) ASCUS/AGUS
Atypia	Koilocytic atypia, flat condyloma, without epithelial changes	Low-grade CIN	LSIL
Mild dysplasia or mild dyskaryosis	CIN 1	Low-grade CIN	LSIL
Moderate dysplasia or moderate dyskaryosis	CIN 2	High-grade CIN	HSIL
Sever dysplasia or severe dyskaryosis	CIN 3	High-grade CIN	HSIL
Carcinoma *in-situ*	CIN 3	High-grade CIN	HSIL
Invasive carcinoma	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

CIN: cervical intraepithelial neoplasia; LSIL: Low-grade squamous intra epithelial lesion; HSIL: High-grade squamous intraepithelial lesion; ASCUS: Atypical squamous cells o f undetermined significance; AGUS: Atypical glandular cells of undetermined significance.

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Table 1

CIN 1 demonstrates undifferentiated cells in the basal layer of the epithelium. It has only minimal nuclear anomalies and sparse mitotic bodies. CIN 2 leads to dysplastic changes occurring in the lower half of the epithelium together with more numerous nuclear anomalies and mitotic bodies. Finally in CIN 3 there is complete disarray with nuclear anomalies and mitotic bodies through the full thickness of the epithelium (Figure 2).

The NHS Cervical Screening programme (NHSCSP) recommends the use of the three-tier terminology for the histological reporting of CIN (CIN1, CIN2, CIN3). The advantages of the three-tier system are that it allowed direct correlation with the cytological grades of dyskaryosis and that it ensured continuity in the recording, transfer, and storage of coded data to existing local, regional, and national databases. Collection and analysis of this data is necessary to evaluate the effectiveness of the cervical screening programme.

CGIN

This article would not be complete without mentioning Cervical Glandular Intraepithelial Neoplasia (CGIN). CGIN is the precursor lesion of a cervical adenocarcinoma. HPV 18 plays a major aetiological role. However, unlike CIN the natural history of CGIN is not well understood. The NHSCSP classification system

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