# Cervical Cancer Screening – An Update

ALBERT CILIA-VINCENTI

In many countries cervical cancer is the commonest gynaecological cancer. In Malta and in the United States, it is the third most common gynaecological cancer. Countries which introduced organised cervical screening programmes saw a dramatic decrease in incidence and mortality from this cancer.[1] In Malta however, its incidence and mortality has remained relatively constant in the last few decades, in keeping with the fact that we lack a national organised call and re-call cervical screening programme.[2] Our cervical screening is largely opportunistic and most of it is carried out in the private sector. Although incidence and mortality has not decreased, our present imperfect screening must however have prevented a significant rise in incidence and mortality, because the detection (and treatment) of premalignant cervical lesions has risen over recent decades, in keeping with increased sexual promiscuity.

Infection with high-risk strains of human papillomavirus (HPV) has been identified as the underlying cause of cervical cancer.[3] However, HPV infection is usually transient and quite common in the general population, with a lifetime cumulative risk of at least 80%.[4,5] Persistent infection by high-risk HPV (most commonly subtypes 16, 18, 31 and 45) is a prerequisite for development of cervical intraepithelial neoplasia (CIN – premalignant lesion), and subsequent malignant transformation to invasive cervical cancer. HPV is a necessary precursor of CIN but does not act alone – host factors such as age, immune status,[6] history of other sexually transmitted diseases[7] and smoking[8] are cofactors.

CIN lesions are usually diagnosed in women younger than 40 years, which is 10 to 15 years earlier than in women diagnosed with invasive cervical cancer, this age gap indicating a long latency period for malignant transformation. Low-grade CIN is usually diagnosed in women in their 20s, whereas high-grade CIN is usually diagnosed in women aged 25 to 35 years, and invasive cancer is most often diagnosed in women older than 40 years.

About 70% of cervical cancer is caused by HPV types 16 and 18. Vaccines have been developed against both HPV 16 and 18 and against low-risk HPV 6 and 11, the latter two being responsible for the majority of genital warts.

Although it is not clear how long immunity will last after vaccination, the

data suggest at least 5 to 6 years.[9,10] Nevertheless vaccinated women are still at risk for cervical cancer related to other less common high-risk HPV types, and it is imperative that vaccinated women should continue screening.

An understanding of the natural history of low-grade and high-grade CIN lesions is central to clinical management of abnormal cervical cytology. Low-grade CIN lesions have poor reproducibility between pathologists, some not even making a distinction between uncomplicated HPV infection changes and low-grade CIN. Unfortunately this is encouraged by the Bethesda System whose low-grade squamous intraepithelial lesion (LSIL) category does not distinguish between pure HPV changes and CIN 1. The cellular abnormalities in teenage girls and women in their early 20s are practically always due to simple HPV infection uncomplicated by CIN, and invasive cervical cancer in this age-group is as rare as hen's teeth. Cytological diagnoses of LSIL in teenage girls may lead to colposcopy, which would amount to over-investigation that is difficult to justify – if this leads to cone biopsy, it would mean even worse management.

Pathology consultation reports should communicate diagnostic opinion to clinicians in clear clinical language and not in laboratory jargon. It is the author's experience that, if clinicians want to know whether their patient has simple HPV infection, low-grade or high-grade CIN, the smear report should use these terms, rather than koilocytosis, dyskaryosis, LSIL, HSIL, etc., to avoid any possible misunderstanding as to the exact pathology the cytology report is suggesting. If the pathologist is uncertain whether the cellular abnormalities are due to non-specific inflammatory reactive hyperplasia, HPV infection or CIN, this uncertainty should be stated in plain English – to the author, Bethesda System diagnostic categories such as "atypical cells of uncertain significance" suggest an inexperienced beginner is issuing the cytology consultation reports.

Clear laboratory reporting should be complimented by adequate clinical information on smear request forms – why? The smears which should be examined most carefully are those from women in their 30s and 40s without a history of regular normal smears, in an effort to cut down, as much as possible, the ever-present risk of the dreaded false-negative smear in a patient with invasive cervical cancer. The cervical cytology request form should therefore, ideally, be designed to prompt the clinician to offer some basic clinical information about the patient, namely, age and whether or not she has a history of regular normal smears. Information about parity is irrelevant because this is not related to risk of cervical cancer, as believed several decades ago.

The screening methods available are the conventional smear, liquid-based cytology (LBC) and HPV DNA (high-risk, not type specific) plus cytology. The reported sensitivity of a single conventional smear varies from 32 to 92%,[11] which prompted the early guidelines for annual smear screening.

LBC has a similar performance record to the conventional smear, and meta-analysis of eight studies demonstrated similar sensitivity and specificity between the two technologies.[12] Thus, either method is an acceptable screening test, and raises the question whether the significantly increased cost of LBC is justified. Furthermore, from the author's experience, the LBC technique leads to under-diagnosis of bacterial vaginosis – a not insignificant condition as it may require antibiotic treatment.[13]

HPV DNA testing, in combination with cytology, is useful in identifying patients with difficult-to-interpret cytological abnormalities who are at increased risk for neoplasia.[14] In this patient category, the negative predictive value of the HPV DNA (high-risk, not type specific) for CIN 2 and CIN 3, or worse, as confirmed by colposcopy, is 99%.[15] Women testing negative on both cytology and HPV DNA can increase their screening interval to 3 years.[16]

A biomarker that distinguishes between low-risk transient HPV infections from high-risk persistent infection might prove more accurate than HPV DNA testing in the above category of women with equivocal cytology. The tumour suppressor gene *p16* is upregulated in high-risk HPV-transformed cells, and 95% sensitivity and 84% specificity in detecting high-grade CIN has been reported.[17] S


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