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CERVICAL CYTOLOGY - XXI CENTURY:

NEW TECHNOLOGY, NEW GUIDELINES"

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INTRODUCTION

Both systemic and opportunistic cytology screening programmes have shown a 60 % to 70% reduction in mortality rates due to cervical cancer. Cervical cytology is not perfect, however, for it suffers from several pitfalls, namely false-negative and false-positive results. These are on average, 50 % and up to 15 %, respectively [1]. The reasons for the relatively low sensitivity and specificity rates are sampling errors and reading/ interpretation errors. In view of these facts, the only way to explain the excellent contribution of conventional cytology toward decreasing cervical cancer incidence and mortality rates is that the test must be frequently repeated. This, however, is a cost-ineffective way to screen for disease.

New technology devices

In recent years, technological advances have been developed for better sample collection, cell processing and interpretation of morphologic alterations. These techniques combined with molecular technology using biomarkers such as HPV genotypes allow for much improved detection rates of cervix cancer and its precursors. Conversely, the very high negative predictive value of new technology-assisted cytology not only meets patients' expectations but also allows for increasing screening intervals, safely. As such, screening programmes utilizing new technology devices such as liquid-based cytology (LBC) and HPV DNA testing are likely to contribute to cost reduction of primary cervix cancer screening programmes. The cumulative sensitivity for detecting HSIL (CIN II/III) in primary cervical cancer screening studies is on average 90 % with HPV DNA testing alone versus 60 % with cytology, and 100 % with the combination of cervical cytology and HPV DNA testing using either hybrid capture or PCR technology [2]. The negative predictive value of the combination approach is close to or at 100 %. It is foreseen that the aforementioned techniques will be suitable to use in computer-assisted automated screening machines [2].

The advantages of LBC are: a) greater availability of potentially diagnostic cells, b) improved disease detection due to significant improvement in the quality of slides (prepared by machine) and c) panel testing for HPV DNA, as well as Chlamydia trachomatis and

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gonococcus (gonorrhea) as well. The advantages of computer-assisted automated cytology are also improved disease detection and either increased volume read or less manpower needed. Automated machines perform as well as humans at a rate of 50 % without human review (of machine-read negative slides) needed. In a 10 % quality control mode, computer-assisted automated cytology performs 5 to 8 times better than humans in detecting false-negative cases of cervical cancer and its precursors [2].

Persistent HPV infection: Role of HPV DNA Testing

The high point prevalence of latent HPV infection among sexually active young women and its dramatic decrease by 30 years of age is evidence of the transient nature of most cases of HPV infection. In contrast, persistent HPV infection over many years leads to genetic alterations, development of precancer and progression of precancer to cervical cancer. As such, persistent HPV infection appears to play a central role in the pathogenesis of cervical cancer. Persistent infection is arbitrarily defined when the same HPV type is detected at least twice over a period of one or more years. Risk factors for persistent HPV infection include increasing age, impaired cell-mediated immunity, genetic predisposition and non-European HPV molecular variants. P53 polymorphism on codon 72 and high viral load may be additional risk factors [3].

Primary screening for HPV DNA detects prevalent infection and when applied at age 30 years and older, identifies those with a persistent type-specific infection. These women are at high risk for either having or developing high-grade cervical precancer. Detection of cervical precancers using hybrid capture technology for HPV DNA assay (HC-II,) is consistently superior to cervical cytology in both primary and secondary screening modes [4,5].

Identification of precancers through cytologic and molecular screening methods and eventually their prevention through HPV vaccination and public health measures will lead to a significant decrease, if not complete eradication of cervical cancer [6].

HPV DNA testing instead of cervical cytology may prove to be attractive for developing and developed but poor countries where neither manpower nor financial resources exist to establish high quality cytology screening programmes. In addition to requiring little technical skills and equipment, HPV testing using hybrid capture technology has the potential to obtain cellular specimens by patients' self-sampling. This in turn may improve compliance of participation in cervical cancer screening programmes [2].

New technologies dictate new guidelines for primary screening and management of women with abnormal versus normal test results (Figure 1).

In addition to primary screening for cervical cancer and its precursors, at present, there are three potential indications for HPV DNA testing [7]. The US-FDA approved "reflex HPV testing" for triaging women with ASC-US (so-called secondary screening). The latter has been suggested to be the preferred option over repeat cytology and immediate colposcopy for detecting H-CIN in women with an initial ASC-US Pap test [8]. Indeed, prospective follow-up studies on a large number of women with an initial ASC-US Pap test showed that HPV DNA testing is at least as good as colposcopy for detecting pre-existent and high-grade CIN3, but refer only 55 % of patients to colposcopy. In addition, HPV DNA testing detects CIN3 earlier than cytology which has to be repeated at least twice to obtain similar sensitivity, however, 14 % more patients must be sent to colposcopy [10]. The other indications include post-treatment follow-up and follow-up of colposcopy/histology negative women whose

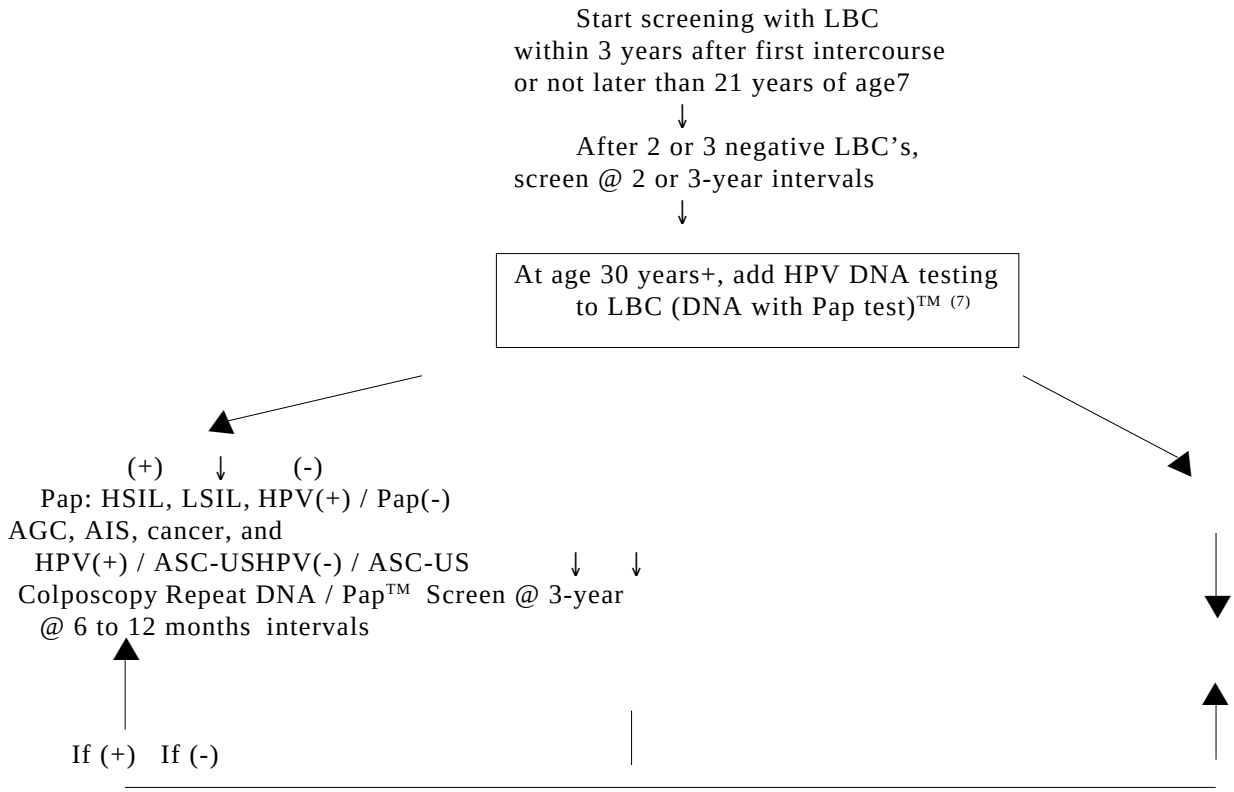

Figure 1. New guidelines for primary screening and management of women with abnormal versus normal test results.
AGC = atypical glandular cells, not otherwise specified, or suspect adenocarcinoma in-situ (AIS)
ASC-US = atypical squamous cells of undetermined significance

initial Pap test was reported ASC-US, atypical squamous cells rule out high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL) or atypical glandular cells not otherwise specified (AGC-NOS) [11]. In the latter two situations, HPV DNA testing is used "off-label". Algorithms for each of the aforementioned indications are available from the consensus guidelines for the management of cervical cytological abnormalities [8].

Overall, HPV DNA testing in both primary and secondary screening modes and follow-up schemes has the potential to make better and more cost-effective management decisions than the repeat cytology programme or colposcopy.

False-positive cytology leading to unnecessary diagnostic triage procedures may be greatly improved by HPV-based diagnostic triage of women with an equivocal (ASCUS) cervical cytology. Half a dozen diagnostic triage studies have shown the diagnostic utility of the combination approach, i.e. cytology and hybrid capture HPV testing, in identifying over 90 % of the small subset of HSIL in women whose initial cytology was ASCUS. As a result, up to 70 % of colposcopies can be deferred.

CONCLUSIONS

The current data support the clinical role of high-risk HPV DNA testing in combination with liquid-based cytology for the detection of pre-existent or subsequent cervical cancer and its precursors. The appropriate routine use of molecular technology for screening and management of women at cervical carcinoma risk should focus on women with persistent HPV infection and its complication (HSIL/CIN and cancer) and mandates for clear guidelines and educational programmes for healthcare providers and patients. Longitudinal studies are needed to provide further insight into the diagnostic yield and potential pitfalls of HPV DNA testing before accepting it as the gold standard for follow-up of women after therapy and latent HPV infections. The ultimate goal is to establish longer and safe screening intervals as per proposed recommendations [(2)]. It is hoped that the money saved by increasing screening intervals will be spent on further clinical research in the field and for urgently needed public awareness campaigns about cervical cancer. This occurs in 471 000 women yearly worldwide; about one-third of them die in industrialized countries and two-thirds die in developing countries within three years of diagnosis of this otherwise preventable disease [(2-5)].

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