COMMENTARY

Cervical Cancer: Screening and Prevention

Nadereh Behtash, Nili Mehrdad

Abstract

Cancer of the cervix is the second most common life-threatening cancer among women worldwide and both incidence and mortality rates are likely to be underestimated in developing countries. HPV high risk strains play at least the major if not an absolutely necessary role in the etiology. The concept of cervical intraepithelial neoplasia (CIN) was introduced in 1968 as an equivalent to the term dysplasia, which means abnormal maturation. Cervical cancer progresses slowly from preinvasive CIN to invasive cancer and therefore screening for dysplasia is an important public health effort worldwide, given the accessibility of the primary organ site, the acceptability of current screening methods, and the long preinvasive period in which to detect disease and successfully intervene. It is widely accepted that detection and treatment of HPV-related dysplastic epithelial change in the form of CIN-2 and CIN-3 can prevent the development of invasive cervical cancer in individual patients. The mainstay of screening programs has been the Pap smear, introduced originally by George Papanicolaou in 1941. However, considerable numbers of false-negative Pap smears may occur with the traditional Pap technique, mostly due to sampling error. More recently, the use of liquid-based technologies such as ThinPrep and AutoCyte Prep have gained popularity, in part because of evidence suggesting reduction in the incidence of inadequate smears. It is also hoped that the ability to identify patients with oncogenic HPV types will lead to improved detection in women more likely to have squamous intraepithelial lesions. Hybrid Capture 2 is the latest refinement of HPV tests and has been described as having enhanced sensitivity. HPV DNA testing can be used as an adjunct to cytology in routine cervical disease screening programs. Establishment of the link between HPV and cervical cancer has further provided the impetus for research into prophylactic vaccination against the most common HPV types associated with the disease, HPV 16 and 18. Initial studies have provided evidence that L1 virus-like particle vaccines against HPV types (as monovalent, bivalent, or quadrivalent vaccines) prevent at least 90% of incident and persistent infections and their associated precursors of cervical cancer. This vaccine has sustained long-term vaccine efficacy against incident and persistent infections and in the long term should provide an answer to the cervical cancer problem. For the vast majority of women who have already been infected, however, continued screening and resection need to be emphasized.

Key Words: Cervical cancer -screening -prevention - vaccination

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Introduction

Cancer of the cervix is the second most common life-threatening cancer among women worldwide, with incidence rates ranging from 4.8 per 100,000 women per year in the Middle East to 44.3 per 100,000 in East Africa (Haverkos, 2005). Both incidence and mortality rates are likely to be underestimated in developing countries. The mean age for cervical cancer is 51.4 years and the most common type is squamous cell carcinoma (Jonathan et al., 2003). Survival rates for cancer of the uterine cervix have improved over the last 40 years largely because of the impact of screening measures (O'Meara, 2002).

Etiology and Risk Factors

HPV-16 and HPV-18 play at least a major if not a necessary role in the etiology of cervical cancer. HPV is not sufficient to induce cervical cancer and a multifactorial etiology is likely. HPV can be found in a growing proportion of patients with cervical cancer, approaching 100%, but may not be identified in every patient with disease (Haverkos, 2005). HPV-16 is the most prevalent, followed by HPV-18, and HPV-33. In a retrospective study, Mortazavi et al (2002) determined the prevalence of HPV-16,18, and 33 in cases of cervical cancer from Iran. The majority of tumors were squamous cell carcinoma (87%) and 73.9% of these were HPV-16 positive; the rest (11.6%) demonstrated type 18 and 33. They concluded that the prevalence of HPV in cervical cancer in Iran is similar to those reported in other regions of the world (Mortazavi et al., 2002). Hamkar et al. reported the prevalence of HPV types in 100 cervical biopsy specimens in Mazandaran province. HPV DNA was detected in 78.6% of cervical carcinoma cases, 64.3% of dys/

*Vali-E-Asr Hospital, Tehran, Iran * For Correspondence: nilimehrdadmd@yahoo.com*

metaplasis and 9% of normal cases.Significant correlation was found between the presence of HPV DNA and development of cervical carcinoma (Hamkar et al., 2002).

Age of coitarche is an important epidemiologic variable in determining risk of cervical neoplasia. The lifetime risk for development of cervical cancer is increased 26-fold if age at first intercourse is within 1 year of menarche, as opposed to 23 years of age or older (Jonathan et al., 2003). Risk factors for the development of cervical cancer in addition to infection with the HPV virus, are low socio-economic status, multiple sexual partners, history of sexually transmitted disease and immunosuppression (John et al ., 2003). Other factors, such as herpes simplex virus type 2 infections, cigarette smoking, vaginal douching, nutrition, and use of oral contraceptives, have been proposed as contributing factors. Long years of inhaling smoke from wood and coal-burning stoves in poorly ventilated kitchens is also proposed as a contributing factor (Haverkos, 2005).

Natural History

The concept of preinvasive disease of the cervix was introduced in 1947, when it was recognized that epithelial changes could be identified that had the appearance of invasive cancer but were confined to the epithelium. If these lesions are not treated, they can progress to cervical cancer. These early precursor lesions are named dysplasia. All dysplasias have the potential for progression. The concept of cervical intraepithelial neoplasia (CIN) was introduced in 1968. This term is equivalent to the term dysplasia which means abnormal maturation (Jonathan et al., 2002). Cervical cancer progresses slowly from preinvasive CIN to invasive cancer.

Signs and Symptoms

Cervical intraepithelial neoplasia (CIN) are asymptomatic and essentially unrecognizable on gross inspection or palpation (John et al., 2003). Abnormal vaginal bleeding is the most common presenting symptom of invasive cancer of the cervix. In sexually active women, this usually includes postcoital bleeding, but there may also be intermenstrual or postmenopausal bleeding. Cervical cancer often is asymptomatic until quite advanced in women who are not sexually active (Jonathan et al., 2003).

Screening

In the endeavour to prevent cervical cancer one must consider the whole chain of events, i.e. population-tests – treatment-outcome. New and improved test methods and treatment procedures are of little use if women refrain from coming for a test when called (Rydstorm et al., 2006). According to Dietrich's study telephone support can improve cancer screening rates among women who visit community and migrant health centers (Dietrich et al., 2006).

Screening for cervical dysplasia is an important public health effort worldwide. In unscreened populations, the incidence of cervical cancer ranges between 2 and 4 % of the adult female population, whereas less than 0.1% of the screened population of Caucasian women has cervical cancer in the United states (Walmer et al., 2004).

Squamous cell cancer of the cervix and its precursor, cervical dysplasia, have been targeted successfully by screening because of the accessibility of the primary organ site, the acceptability of current screening methods, and the long preinvasive disease state in which to detect disease and successfully intervene. It is widely accepted that detection and treatment of HPV-related dysplastic epithelial change in the form of CIN-2 and CIN-3 can prevent the development of invasive cervical cancer in individual patients (O'Meara 2002).

In the developed nations, reductions in cervical cancer mortality have been attributed to the institution of widespread screening for cervical cancer precursors. The mainstay of these screening programs has been the Pap smear, introduced originally by George Papanicolaou in 1941. Ideal screening tests are cost-effective, minimally invasive, and acceptable to patients, and are able to detect disease in a preinvasive or early invasive state, when the process is more easily curable (O'Meara 2002).

The standard technique for collecting a Pap smear is to sample the cervical portio and endocervical canal, usually with the combination of a spatula and an endocervical brush, and to smear these samples onto a slide in the office and immediately fix the smear with cytology fixative. The foci of clinicians in the collection of the sample are the minimization of sampling error through effective sampling of the transformation zone (to include endocervical cells) and the elimination of drying artifact through rapid fixation. Despite these efforts, false-negative Pap smears occur with this traditional Pap technique at least 20% of the time, with most of those false-negative caused by sampling error (O'Meara 2002). Annual cervical cancer screening in women with many prior normal Pap tests is common despite limited evidence on the cost-effectiveness of this strategy. Kulsingam et al estimated the cost-effectiveness of screening women with 3 or more prior normal tests compared with screening those with no prior tests They concluded that as the number of prior normal tests increased, the cost per life years saved increase substantially. Resources should be priorized for screening those never or rarely screened women(Kulasingam et al. 2006).

A high rate of false-negative smears and of atypical squamous cells(ASC) diagnoses have led to the development of new diagnostic techniques (Giovanni et al. 2003). More recently, the use of liquid-based technologies such as ThinPrep and AutoCyte Prep have gained popularity, in part because of evidence suggesting reduction in the incidence of inadequate smears. In these methods, the cervix is sampled in the same way as in the traditional Pap smear, but the sampling device is placed in a liquid medium for transport to the laboratory, where the cells are collected by extraction across a filter (ThinPrep) or through layering onto a density

reagent (AutoCyte Prep) and plated evenly on a slide for review. The beneficial results for the reviewer of the slide include decreased debris and red blood cells on the slide, reduction in cellular distortion, and a more even distribution of cells (O'Meara 2002). The ThinPrep Pap test was approved for marketing based on studies showing an increase in the detection of LSIL or worse from a rate of 8% by conventional Pap smear to a rate of 9.4% by ThinPrep (O'Meara, 2002). Increased rates of squamous intraepithelial lesion (SIL) diagnosis with liquid-based cervicovaginal cytology methods are well documented (Baker, 2002).

Sangwa-Lugoma et al evaluated the feasibility and performance of visual inspection with acetic acid (VIA) and lugol's iodine (VILI) for cervical cancer screening in a primary health-care setting in Kinshasa, Congo. They concluded that VIA and VILI performed by nurses and physicians are slightly more sensitive but less specific than Pap cytology across multiple combinations of test and lesion thresholds. Given their lower cost and easy deployment, visual inspection methods merit further assessment as cervical cancer screening methods for low-resource countries (Sangwa-Lugoma et al., 2006). Ghaemmaghami et al. estimated the sensivity and specificity of visual inspection of the uterine cervix with acetic acid as a screening test for cervical carcinoma and its precursors. In this study, the sensivity and specificity of VIA were high and comparable with those of cytology. Hence, VIA can be undertaken as a feasible method of screening in cervical cancer in countries where access to cytopathology is limited (Ghaemmaghami et al., 2004).

Bypassing cytology and going directly to colposcopy has been successfully implemented as a screening strategy for dysplasia in low resource settings. Walmer et al (2004) described the development and utilization of a portable binocular colposcope that does not require electricity.

It is hoped that the ability to identify patients with oncogenic HPV types will lead to improved detection in women more likely to have SILs. The potential value of HPV testing for cervical cancer and its precursors is based on this association. Hybrid Capture 2 is the latest refinement of HPV tests and has been described as having enhanced sensitivity. It can detect 13 high-risk types of HPV. The sample is collected with a cervical swab of the transformation zone and placed into transport medium. The test may also be performed from residual material collected in liquid-based medium for mono-layer preparation (Jim et al. 2001). In the laboratory, cellular DNA is denatured and mixed with a ribonucleic acid probe that binds only to HPV DNA (Jim et al. 2001). The DNA "hybrid" is then captured by antibodies coating the sides of the tube. Next, a chemical is added, causing a chemoluminescent reaction. The amount of light that is measured can be used to determine the presence of HPV and the viral load (Jim et al., 2001). HPV DNA testing can be used s an adjunct to cytology in routine cervical disease screening programs (Lorincz 2003). As an adjunct to the Pap cytology test in routine screening, HPV DNA testing is a more sensitive indicator for prevalent high-grade CIN than either conventional or liquid cytology (Lorincz 2003). A combination of HPV DNA and Papanicolaou testing had almost 100% sensitivity and negative predictive value.The specificity of the combined tests is slightly lower than the specificity of the Papanicolaou test. One "double-negative" HPV DNA and Papanicolaou test indicated a higher prognostic assurance against risk of future CIN3 than three subsequent negative conventional Papanicolaou tests and may safely allow three-year or longer screening intervals for such low-risk women.It appears that HPV DNA testing is on the way to becoming a common testing strategy in cervical cancer prevention programs (Lorincz 2003). Each of the new techniques will increase the costs of routine Pap smear testing. Whether these costs are justifiable is controversial (Jim et al. 2001).The cost-effectiveness of conventional Pap smear screening every three years compared with no Pap smear screening was $4.079 per life-year saved (Jim et al. 2001). The addition of new screening technology every three years had an incremental cost of $22.010, which was less than the usually accepted threshold of $50.000 per life-year saved (Jim et al. 2001). How should the clinician respond to these proposed measures to improve the detection rate of cervical cancer and its precursors? Specific recommendations for practicing clinicians are listed in Table 1.

Behtash et al determined the reasons leading to an inappropriate simple hysterectomy in the presence of invasive cervical cancer. During 1997-2001, 62 cases of invasive cervical carcinoma that had been treated by simple hysterectomy were referred to the gynecology oncology service in Vali-e-Asr hospital, Tehran, Iran. Reasons for inappropriate hysterectomy were as follows: lack of preoperative Pap smears (29%), deliberate hysterectomy for biopsy-proven cancer (25.8%), negative Pap smear (6.5%), inadequate evaluation of abnormal Pap smear (6.5%), failure to perform an indicated conization (3.2%), and emergent operation because of uterine perforation (1.6%). Reasons for inappropriate hysterectomy in the remainder of patients (27.4%) were not found because of lack of sufficient information. Although 45.2% of these patients had complained of vaginal bleeding, only four of them had preoperative endocervical and endometrial sampling. This necessitates some reconsideration of gynecological oncology postgraduate courses for general gynecologists (Behtash et al., 2003).

Table 1. Recommendations to Improve the Detection of Cervical Cancer and its Precursors

Ensure proper technique in sample selection.
Implement measures to improve compliance with cervical cancer screening.
Advocate for access to care for the unscreened population.
Ensure that treatment of cervical disease follows acceptable guidelines emphasizing cytologic, colposcopic, histologic correlation.

Vaccination

Establishment of the link between HPV and cervical cancer has provided the impetus for research into prophylactic vaccination against the most common HPV types associated with the disease- HPV 16 and 18. Initial studies have provided evidence that L1 virus-like particle vaccines against HPV 16 and HPV 18 (as monovalent, bivalent, or quadrivalent vaccines) prevent at least 90% of incident and persistent infections and their associated precursors of cervical cancer. Background effective vaccination against HPV 16 and HPV 18 to prevent cervical cancer will require a high level of sustained protection against infection and precancerous lesions (Harper et al. 2006). Harper et al assessed the long-term efficacy, immunogenicity, and safety of a bivalent HPV-16/18 L1 virus-like particle ASO4 vaccine against incident and persistent infection with HPV 16 and 18 and their associated cytological and histological outcomes. They did a follow-up study of their multicentre, double-blind, randomised, placebo-controlled trial. They included women who originally received all three doses of bivalent HPV16-/18 virus- like particle ASO4 vaccine (0.5 ml; n=393) or placebo (n=383).They assessed HPV DNA, using cervical samples, and did yearly cervical cytology assessments. They also studied the long-term immunogenicity and safety of the vaccine (Harper et al. 2006). Up to 4.5 years, the HPV 16/ 18 L1 virus-like particle ASO4 vaccine was highly immunogenic and safe, and induced a high degree of protection against HPV-16/18 infection and associated cervical lesions. Their findings indicated that the HPV16/ 18 L1 virus-like particle ASO4 vaccine has sustained long-term vaccine efficacy against incident and persistent infections associated with HPV 16 and HPV 18. Their results showed sustained immune response and long-term efficacy against HPV16 and HPV18 infection, including persistence up to 12 months, and against related cytological outcomes as well as providing evidence of broader protection against cytohistological outcomes.

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