MINI-REVIEW

Cervical Cancer and HPV Vaccines in Developing Countries

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Abstract

Cervical cancer is the second most common cancer among women in the world. Despite a decline of up to 70% in its incidence and prevalence through screening programs, it is still the most common gynecological cancer worldwide. Since the human papilloma virus (HPV) was conclusively identified as the etiological factor inducing cervical cancer, investigations during the last two decades have been concentrating on producing a vaccine against HPV virus. Thus prevention of HPV infection has been the main purpose and vaccination is expected to reduce up to 70% of related cervical cancer and prevent precancerous and cancerous lesions of the genitalia. However, screening programs are still essential for those who have already been exposed to the high risk forms of the virus and educational and information programs continue to play important roles to increase the success rate of screening, by whichever of the modalities is most appropriate for the local conditions.

Key Words: Cervical cancer - vaccination - HPV - screening - prevention

Asian Pacific J Cancer Prev, **10**, 969-974

Introduction

Cervical cancer is the second most common cause of death among women with various cancers. In 2006, about 500,000 new cases of cervical cancer were reported and it was predicted that 280,000 of them led to death. Most of these cases have been reported from developing countries in Africa, Central America, and South America in which there is no organized programs for screening and early diagnosis (Society of Gynecologic Oncologists statement on cervix cancer vaccine, 2006).

Cervical cancer is the most common gynecological cancer in Iran (Behtash et al.,2005), where various methods of screening, diagnosis, and treatment hav been reported (Behtash et al., 2003; 2005; 2006; Nazari et al., 2006; Mousavi and Karimi Zarchi , 2007; Ghaemmaghami et al.,2008; Mousavi et al., 2008). However, since there is no lucid system to document the data on cancers, there are no clear reports of incidence and prevalence of cervical cancer in Iran. The Cancer institute has reported a 6-7/ 100,000 prevalence for cervical and endometrial cancers with a peak at 30-55 years of age, although there have been several reports of younger age involvement. During the last 50 years in the Westrn world there has been a decline of 70% in prevalence and incidence and also mortality of this cancer owing to the screening programs and regular Pap smear testing.

HPV Infection

Until 1997, it was widely believed that HPV infection, like other genitalia infections, is only a predisposing factor for cervical cancer. However, after 2000, the virus was confimed as the main etiological factor, which makes cervical cancer the only cancer in women with a clear viral etiology. HPV viruses act via inhibition of apoptosis (programmed cell death) and producing proteins to restrain P53 and retinoblastoma (cell growth inhibition) genes (Behtash et al., 2002; 2003).

More than 40 types of HPV viruses has been indentified which are able to infect vaginal mucosa, but only 15 of them are high risk and cause cancer or precancerous lesions such as CIN III. The most common types of HPV virus which cause cervical cancer are types 16 and 18 which have been detected in 60% and 10-20% of cervical cancers respectively (Munoz et al., 2003; Castellsague et al., 2006). It is important to note that HPV has also been detected in 30% of oropharynx cancers, 45-95% of anal cancers, 60-65% of vaginal cancers, and 40-60% of vulvar cancers (Schiffman et al., 2003; Daling et al., 2004). Independent factors which increase the risk of cervical cancer are: starting sexual activity at young age, multi-parity, multi partners, cigarettes, and HIV (human immunodeficiency virus) infection (Daling et al., 2004). HPV infection is well known to be a sexually transmitted disease and therefore its rate is higher among individuals with multiple partners.

Women with permanent HPV infections are at higher risk of developing precancerous lesions or cervical cancers (Munoz et al., 2003; Castellsague et al., 2006). Therefore, factors like smoking which impact on the immune system can influence the likelihood of cancer development.

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Developmental Processes of Cervical Cancer

The structure of the cervix is unique. It comprises two different epithelia; squamous and columnar in which they fuse together at the squamo-collumnar junction (SCJ). During puberty, squamous cells are covered by a new type of tissue (immature metaplasic tissue) which creates a new area called the transformation zone (TZ). Most of the cervical cancers, which are squamos cell cancer, are generated from this area. Infection with HPV virus changes the immature metaplasic tissues to displasic tissues. The neoplasic mass gradually progresses and involves more of basal membranes. The neoplasic steps are: CIN I, CIN II, CIN III , carcinoma in situ (CIS) and invasive cervical cancer, respectively. It has been observed that take about 10-15 years to develop an invasive carcinoma from HPV infection (Daling et al 2004;. Schiffman et al .,2003). It has also been confirmed that the majority of CIN I and about 2/3 of CIN II and CIN III are improved while most of the CIS cases progress into invasive carcinoma (Freeman et al.,2005; Jemal et al.,2006). HPV infection is particularly common among young western women. In America, 70% of adolescence with sexual activity is infected with HPV virus. One study demonstrated that 32% of women aged between 16-24 years old have DNA of HPV virus while this rate declines to just 4% among 45 years old women. In more recent study, the incidence of HPV infection was reported 36% in women age 25 or younger and 2.8% in women age 45 or older. The incidence of HPV infection is very high in young women with high sexual activity in which about 64% of them carry DNA of HPV virus (Freeman et al., 2005).

The incidence of cervical cancer in many countries is less than 10 in 100,000 and it seems that minority of HPV infections develop into the cervical cancer. The risk factors which accelerate this process are: infection with high risk sub-types of HPV virus, prolonged HPV infection for more than two years, HPV infection after 30 years of age, multi partners, HIV infection, smoking, and other environmental influences.

Preventive Role of Screening

Although it has been 50 years since first Papanicolaou test (Pap test) was performed, cervical cancer still causes mortality and morbidity among women in America and other countries. Screening with cytology has decreased the incidence of mortality in developed countries whilst in developing countries and Iran, although the Pap test is performed, in many cases the sever form of cervical cancer is still reported (Behbakht et al., 2004).

The aim of screening with cytology is to detect the cancer and precancerous lesions, whilst with Pap test the surface and falling cells of cervical is evaluated microscopically (Cooper et al., 2005). The screening tests have been universally and successfully performed on many women but the value of screening with cytology is limited. The sensitivity of this method is 30-87% with specificity of 68-100% (Behbakht et al., 2004; Cooper et al., 2005).

The reasons for variable sensitivity and specificity could be due to: small lesions, unsuitable samples, and contamination with blood or cervical discharges. Because of low sensitivity of Pap test, this test has been replaced with liquid based cytology (LBC) in many screening programs (Cooper et al., 2005). Cytology based on liquid increases the chance of detecting the high grade lesions; however, its specificity for these lesions is low. In some studies, using cytology based on liquid method increases the reports of atypical squamous cells of undetermined significance (ASCUS) (Behbakht et al., 2004; Cooper et al., 2005; Hoyo et al., 2005). Testing for DNA of HPV virus is another method in which can compensate for low sensitivity of Pap test. This test is not appropriate to utilize as primary test for screening since meta-analysis data have shown that although HPV DNA test is more sensitive than cytology, its specificity is very low. On average the sensitivity and specificity of HPV DNA test being 85% and 84% respectively in comparison to cytology test with 60% sensitivity and 95% specificity (Kjaer et al., 2002; Wright Jr et al., 2003; Jacobs et al., 2005). However, the HPV DNA test becomes more desirable after the age of

Table 1. Guidelines for Cervical Cancer Screening

Guide line	American Cancer Society	ACOG*	USPSTF**
Starting time of screening	3 years after first intercourse but no later than 21 years of age	3 years after first inter-course but no later than 21	3 years after first intercourse but no later than 21
Screening interval <30 years	With Pap test: yearly With cytology: every two years	Yearly	Yearly
Screening interval ≥ 30	Every 3 years if 3 previous tests were normal	Every 2-3 years if 3 previous tests were normal	Every 2-3 years if 3 previous tests were normal
DNA test of HPV virus as screening	In women ≥ 30 years of age, every 3 years with cytology	In women ≥ 30 , every 3 years with cytology (based on one suggestion)	No clear evidence
Ending time of screening	Women ≥ 70 years of age if 3 previous tests were normal and no abnormal reports in 10 years	There is no clear evidence and no suggestion for ending age	Women >60 if pap tests were normal and proper screening were performed

[a]High risk group including: women who have been exposed to DES, or infected with HIV or are immune deficient should be screened yearly; *American College of Obstetrics and Gynecology, 2003; **U.S. Preventive Services Task Force

30 years. According to the American College of Obstetrics and Gynecology(ACOG) and American cancer society(ASC), the HPV DNA test can be used in accompany with cytology of cervical as screening tests but if at or after 30 years of age both of these tests were negative it would be possible to increase the interval of screening into every three years since the sensitivity and diagnostic value of these tests are very high especially in symptomatic patients (Table1) (Einstein et al., 2002; Kjaer et al., 2002; Wang et al., 2004; Castle et al., 2005; Khan et al., 2005; Kyndi et al., 2006). If cytology of cervical is normal but the HPV DNA test (the cancerous form) is positive the screening should whenever possible be repeated.

Although the screening tests play an important role in decreasing the rate of cervical cancer, in developing countries the cancer is still a big issue in which most of the women develop the progressive form of cervical cancer had no or improper screening. The value of screening is to follow the abnormal results with colposcopy biopsy and start the appropriate treatments based on biopsy results.

The recommendations by ASC and ACOG and U.S. Preventive Services Task Force (USPSTF) are shown in Table 1 (American College of Obstetrics and Gynecology, 2003; Announcement of the Society of Gynecologic Oncologists, 2006). The recent recommendation is to start the screening at 21 years old or 3 years of first sexual activity. Until age of 30, screening should be performed every 1-2 years (based on the method used). On the other hand, if the patient is in a low risk group after 30 years of age the interval of screening can be increased to every 2-3 years (Clavel et al., 1999; Nanda et al., 2000; Belinson et al., 2001; Bernstein et al., 2001; Marino et al., 2001; Obwegeser et al., 2001).

Screening in Adolescents and Young Adults

The incidence of HPV positive is high in young women(Saslow et al.,2002; American College of Obstetricians and Gynecologists., 2003). In one investigation on 1,075 women age between 15-19 years during 5 years 60% of cases were HPV positive (Bundrick JB et al.,2005). Despite the high incidence of HPV infection among this group, most of the infections have been transient and accompanied with just Low grade Squamous Interaepithelial Lesion (LSIL). However, the cytological abnormalities are increasing among young women. In several studies the incidence of ASCUS and LSIL in adolescence were reported 7-16% and 3-13% respectively, whilst this rate for High grade squamous intraepithelial lesions (HSIL) were 2-3% (Cuzick et al., 1991; 2003; Jacobs et al., 2000; Clavel et al., 2001; Kulasingam et al., 2002). Since the incidence of invasive cervical cancer is very rare in this group, and also because of some severe side effects of dysplastic treatment and excisional biopsy, it is recommended that these screening tests are performed with caution and they should based on true history of cervical dysplasia (Cuzick et al., 1991; Schneider et al., 2000; Blumenthal et al., 2001; Franco et al., 2003).

Prophylaxis with Vaccines containing Virus-like Particles of HPV

Vaccination is a cost-effective method to prevent the disease especially infectious agents. The most important aim of HPV vaccine is to reduce the incidence of cervical cancer and precancerous lesions. The other aim is to decrease the rate of cancers and other benign lesions related to HPV infection (Cuzick et al., 1991; Clavel et al., 2001).

There have been two HPV vaccines against HPV and CIN with proven lasting effects of 2 and 4.5 years. These vaccines are: quadrivalent form or Gardasil and bivalent form or Cervarix. Both vaccines contain virus-like particles of HPV types 16 and 18 which cause 70% of all cancers world wide (Franco et al.,2003; Schneider et al.,2000; Blumenthal et al.,2001; Sherman et al.,2003; Wright et al.,2004). Gardasil vaccine also contains virus-like particles of VLP type 6 and 11 which cause vaginal warts. Both vaccines have protein capsidal but no DNA or RNA which makes them unable to infect the person while provokes the immune system and produces antibodies against HPV. In Iran use of this vaccine isn't cost effective and recommend to women that screen only by cytology.

Gardasil Quadrivalent: This vaccine is effective on types 11,6,18 and 16 of HPV virus and contains aluminum as adjuvant (Villa et al.,2005). This vaccine has been examined on 25000 girls and women aged 9-26 and also on 500 men aged 9-15 years old. The end point of evaluations on vaccine efficacy was to determine all different kind of HPV infections and cervical dysplasia. This vaccine contains 20 mg of HPV type 16-18 and 40 mg of 11-16. Its volume is 0.5 ml and should be administrated intramuscularly. The vaccine should be used at 0-2-6 month intervals. All the evaluations have been demonstrated that Gardasil vaccine is effective in prevention of cervical lesions caused by HPV virus types 6-11-16-18 and also decreases the need for technical interventions to diagnose and treat this infection.

During 30 months of follow up, the incidence of prolong infection in people who received at least one dose of this vaccine in comparison to control group who received no vaccine at all was 89%. This rate reaches to 100% in diseases such as: Cervical Intraepithelial Nopelasia (CIN), Vaginal Intraepithelial Neoplasia (VAIN),Vulvar Intraepithelial Neoplasia(VIN), warts of genitalia, and invasive cervical cancer in which their diagnosis is based on biopsy. The protective duration of vaccine is 3.5 years for type 16 after completing one period of vaccination and is 2.5 years for types 6-11-18 after completing three periods of vaccination. Gardasil is well tolerated in women age 9-26 years old although some side effects such as pain and/or bleeding at injection site, and low grade fever has been reported. Headache has been reported as the most common systemic side effect of the vaccine. The Gardasil vaccine has been proved by FDA (Food and Drug association of America) for women and young adult age 9-26 years old and in Year 2006 the vaccine has also been recommended to use as early as

11-12 years of age although it is safe to use at even earlier age of 9. The purpose of these recommendations of early vaccination is to immunize the young girls before they begin their sexual activity(Villa et al.,2005). However, this vaccine can be beneficial even in young sexually active women who have not been immunized before and it should therefore be routinely used in women age between 13-26 years. In general the vaccination should be used for women, 9-26 years old, who had an abnormal Pap test or genital warts or positive HPV test for high risk virus. The efficacy of vaccine to provide immunization has been confirmed, but there still no evidence of its therapeutic effects on cervical-vagina lesions(Villa et al., 2005; Harper et al., 2006 ; Mao et al.,2006; Frisch et al.,2000).

The vaccine can be used in women with immune system deficiency because of high risk of HPV infection in this group; however, since there is no clear evidence of its advantage, it should be used with caution especially in women who are at risk of developing Graft-Versus Host disease. Vaccination should be avoided during pregnancy. If a pregnant woman received vaccination accidentally her fetus might be at risk of some minor congenital anomalies. Vaccination is safe during breast-feeding but the mothers should be educated about respiratory distress that might occur after about one month of vaccination. The allergic reaction might also occur after vaccination (Frisch et al., 2000; Blumenthal et al., 2001; Sherman et al., 2003; Wright et al., 2004; Villa et al., 2005; Harper et al., 2006; Mao et al., 2006).

Bivalent form of HPV vaccine (Cervarix): This vaccine contains particles of type 16-18 of HPV virus. Its adjuvant is aluminum and contains lipid. The efficacy of this vaccine has been examined on 27000 girls and women age 11-55 years but it has not been examined on men yet. The end point of these evaluations was to determine the infections related to the certain type of HPV virus. This vaccine contains protein capcid with no DNA cover. The virus is not alive but can provoke immune system to produce antibodies against HPV virus. The investigations during 2004-2006 demonstrated that vaccination using bivalent vaccine is effective to reduce the HPV related infections (Wright et al., 2004; Villa et al., 2005). In year 2004, a significant decline has been observed in incidence of HPV-16 and HPV 18. These studies demonstrated an efficacy of 95.1% of vaccine against HPV permanent cervical infections. Even efficacy of 100% has been reported against CIN lesions related to HPV infection. This vaccine is also effective to reduce the rate of infections cause by types 45 and 31 of HPV virus (Harper et al., 2006). The side effects of the vaccine includes: fatigue, gastrointestinal disorders, low grade fever, and headache. There is no clear evidence of protective period of bivalent vaccine but it is still less that ideal time which is few decades from beginning to the end of the sexual activity (Mao et al., 2006). The protective effect of vaccine begins one month after third and final injection and after 18 months reaches to a plateau state (Sherman et al., 2003; Wright et al., 2004; Villa et al., 2005; Harper et al., 2006; Mao et al., 2006). An increase of 133 times in average level of antibodies against HPV-16 and HPV-18 has been observed after 4.5 years of final injection of bivalent vaccine (Mao et al.,2006). Quadrivalent vaccine within 36 months increases the level of antibody against HPV virus even higher than the serum level of these antibodies in women who have been infected with HPV virus (Villa et al.,2005).

Should be HPV Vaccination Performed on Men too?

Since HPV infection is one of sexually transmitted diseases which can be transmitted by both women and men, vaccination is therefore recommended for both sexes. However, the efficacy of HPV vaccine on men is still unclear and needs more evaluation (Harper et al., 2006; Mao et al., 2006).

Is HPV vaccine able to prevent anogenital infections in HIV infected patients? The effectiveness of vaccine in this group of patients is not apparent but the important issue is to provide proper educations for patients, their family and other people related to them (Frisch et al., 2000).

Conclusion

Prevention of HPV infection has been the main purpose of recent investigations. Vaccination is able to reduce up to 70% of cervical cancer related to HPV infection and even prevents precancerous and cancerous lesions of the genitalia. Screening program is essential to prevent cervical cancer and more works are underway to improve screening and perform vaccination against HPV. However, educational and informative programs play an important role to increase the success rate of screening.

References

American College of Obstetricians and Gynecologists (2003). ACOG practice Bulletin 45: Cervical Cytology Screening. *Obstet Gynecol*, **102**, 417-27.

Announcement the Society of Gynecologic Oncologists (2006). Statement on a Cervix Cancer Vaccine. *Gynecol Oncol*, **101**, 377.

Behbakht K, Lynch A, Teal S, et al (2004). Social and cultural barriers to Papanicolaou test screening in an urban population *Obstet Gynecol*, **104**, 1355-61.

Behtash N, Ghaemmaghami F, Ayatollahi H, et al (2005). A case control study to evaluate urinary tract complications in radical hysterectomy. *World J Surg Oncol*, **3**, 12.

Behtash N, Mousavi A, Mohit M, et al (2003). Simple hysterectomy in the presence of invasive cervical cancer in Iran. *Int J Gynecol Cancer*, **13**, 177-81.

Behtash N, Nazari Z, Ayatollahi H, et al(2006). Neoadjuvant chemotherapy and radical surgery compared to radical surgery alone in bulky stage 11b-11A cervical cancer. *Eur J Surg Oncol*, **32**,1226-30.

Belinson J, Quo YL, Pretorius R, et al (2001). Shanxi Province cervical cancer screening study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. *Gyncecol Oncol*, **83**, 439-44.

Bernstein SJ, Sanchez-Ramos L, Ndubisi B (2001). Liquid-based

cervical cytologic smear study and conventional Papanicolaou smears: a meta-analysis of prospective studies comparing cytologic diagnosis and sample adequacy. *Am J Obstet Gynecol*, **185**, 308-17.

Blumenthal PD, Gaffikin L, Chirenje ZM, et al (2001). Adjunctive testing for cervical cancer in low resource settings with visual inspection, HPV, and the Pap smear. *Int J Gynaecol Obstet*, **72**, 47-53.

Bundrick JB, Cook DA, Gostout BS (2005). Screening for cervical cancer and initial treatment of patients with abnomal results from papanicolaou testing. *Mayo Clin Proc*, **80**, 1063-8.

Castellsague X, Diaz M, De Sanjose S, et al (2006). Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. *J Natl Cancer Inst*, **98**, 303-15.

Castle PE, Solomon D, Schiffman M, et al (2005). Human papilloma virus type 16 infections and 2-year absolute risk of cervical precancer in women with equivocal or mild cytologic abnormalities. *J Natl Cancer Inst*, **97**, 1066-71.

Clavel C, Masure M, Bory JP, et al (1999). Hybrid capture 11-based human papillomavirus detection, a sensitive test to detect in routine high-grade cervical lesions: a preliminary study on 1518 women. *Br J Cancer*, 80, 1306-11.

Clavel C, Masure M, Bory JP, et al (2001). Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: a study of 7932 women. *Br J Cancer*, **84**, 1616-23.

Cooper CP, Saraiya M, McLean TA, et al (2005). Report from the CDC. Pap test intervals used by physicians serving low-income women through the national breast and cervical cancer early detection program. *J Womens Health*, **14**, 670-8.

Cuzick J, Szarewski A, Cubic H, et al (2003). Management of women who test positive for high-risk types of human papillomavirus: the HART study. *Lancet*, **362**, 1871-6.

Cuzick J, Beverley E, Ho L, et al(1999). HPV testing in primary screening of older women. Br J cancer , 81, 554-558.

Daling JR, Madeleine MM, Johnson LG, et al (2004). Human papilloma virus, smoking, and sexual practices in the etiology of anal cancer. *Cancer*, **101**, 270-80.

Einstein MH, Cruz Y, El-Awady MK, et al (2002). Utilization of the human genoume sequence localizes human papillomavirus type 16 DNA integrated into the TNFAIP2 gene in a fatal cervical cancer from a 39-year old woman. *Clin Cancer Res*, **8**, 549-554.

Franco EL (2003). Primary screening of cervical cancer with human papillomavirus tests. *J Natl Cancer Inst Monogr*, **31**, 89-96.

Freeman HP, Wingrove BK (2005). Excess cervical cancer mortality: a marker for low access to health care in poor communities. In: institute NC, editor. Rockville, MD: Center to Reduce cancer Health Disparities,345-400.

Frisch M, Biggar RJ, Goedert JJ (2000). Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst*, **92**, 1500-10.

Ghaemmaghami F, Karimi Zarchi M, Mousavi A et al (2008). Results of cervical cone excision biopsy in Iran. *Asian Pac J Cancer Prev*, **9**, 45-7.

Harper DM, Franco EL, Wheeler CM, et al (2006). Sustained efficacy up to 4-5 years of a bivalent Ll virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up form a randomized control trial. *Lancet*, **367**, 1247-55.

Hoyo C, Yarnall KS, Skinner CS, et al (2005). Pain predicts non-adherence to pap smear screening among middle-aged African American women. *Prev Med*, **41**, 439-45.

Jacobs EA, Karavolos K, Rathouz PJ, et al (2005). Limited English proficiency and breast and cervical cancer screening in a multiethnic population. *Am J Public Health*, **95**, 1410-6.

Jacobs MV, Walboomers JM, Snijders PJ, et al (2000). Distribution of 37 mucosotropic HPV types in women with cytologically normal cervical smears: the age-related patterns for high-risk and low-risk types. *Int J Cancer*, **87**, 221-7.

Jemal A, Siegel R, Ward E, et al (2006). Cancer statistics 2006; *CA Cancer J Clin*, **56**, 1006-30.

Khan MJ, Castle PE, Lorincz AT, et al (2005). The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type specific HPV testing in clinical practice. *J Natl Cancer Inst*, **97**, 1072-9.

Kjaer SK, Van Den Brule AJC, Paull G, et al (2002). Type of persistence of high risk human papillomavirus (HPV) as indicator of high grade cervical squamous intraepithelial lesions in young women: population based prospective follow up study. *BMJ*, **325**, 572-6.

Kulasingam SL, Hughes JP, Kiviat NB, et al (2002). Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: comparison of sensitivity, specificity, and frequency of referral. *JAMA*, **288**, 1749-57.

Kyndi M, Frederiksen K, Kruger-Kjaer S (2006). Cervical cancer incidence in Denmark over six decades (1994-2000). *Acta Obstet Gynecol Scand*, **85**, 106-111.

Marino JF, Fremont-Smith M(2001). Direct-to-vial experience with autoCyte PREP in a small New England cytology practice. *J Reprod Med*, **46**, 353-8.

Mao C, Koutsky LA, Ault KA, et al (2006). Efficacy of human papillomaviurs-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. *Obstet Gynecol*, **107**, 18-27

Munoz N, Bosch FX, De Sanjose S, et al (2003). Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med*, **348**, 518-27.

Mousavi A, Karimi Zarchi M, Gilani MM, et al (2008). Radical hysterectomy in the elderly. *World J Surg Oncol*, **6**, 38.

Mousavi A, Karimi Zarchi M (2007). Isolated cervical metastasis of breast cancer: a case report and literature review. *J Low Genit Tract Dis*, **11**, 276-8.

Nanda K, McCrory DC, Myers ER, et al (2000). Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med*, **132**, 810-9.

Obwegeser JH, Brack S (2001). Does liquid-based technology really improve detection of cervical neoplasia? A prospective, randomized trial comparing the ThinPrep Pap Test with the conventional Pap Test, including follow-up of HSIL cases. *Acta Cytol*, **45**, 709-14.

Saslow D, Runowicz CD, Solomon D, et al (2002). American Cancer society guideline for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin*, **52**, 342-62.

Schiffman M, Kjaer SK (2003). Natural history of anogenital human papilloma virus infection and neoplasia. *J Natl Cancer Inst Monogr*, **31**, 14-9.

Schneider A, Hoyer H, Lotz B, et al (2000). Screening for high-grade cervical intra-epithelial neoplasia and cancer by testing for high-risk HPV, routine cytology or colposcopy. *Int J Cancer*, **89**, 529-534.

Sherman ME, Lorincz AT, Scott DR, et al (2003). Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year Cohort analysis. *J Natl Cancer Inst*, **95**, 46-52.

Villa LL, Costa RL, Petta CA, et al (2005). Prophylactic

quadrivalent human papillomavirus (type 6, 11, 16 and 18) Ll virus-like particle vaccine in young women: a randomized double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol*, **6**, 271-8.

Wang SS, Sherman ME, Hildesheim A et al (2004). Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976-2000. *Cancer*, **100**, 1035-44.

Wright Jr TC, Schiffman M (2003). Adding a test for human papillomavirus DNA to cervical-cancer screening. *N Engl J Med*, **348**, 489-90.

Wright TC, Schiffman M, Solomon D, et al (2004). Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. *Obstet Gynecol*, **103**, 304-9.