Updates on Cervical Cancer

Moving forward in prevention, detection and treatment

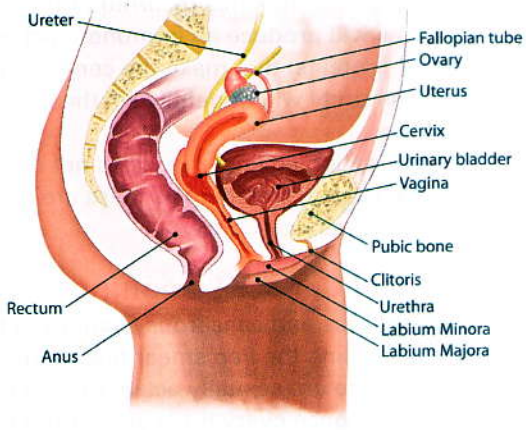
by Dr Lynette Ngo

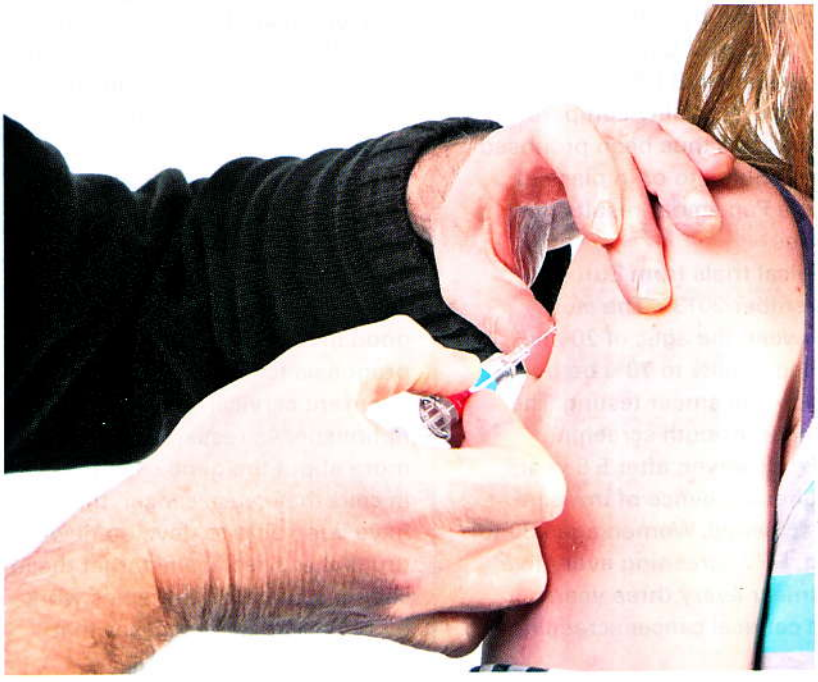
Cancer is the leading cause of death in Singapore. Cervical cancer is the 10th most common cancer affecting Singaporean women today. Thanks to Pap smear screening and improved treatment techniques, the incidence of cervical cancer has decreased dramatically. Over 200 new cases of cervical cancer continue to be diagnosed each year with almost 100 women dying from cervical cancer each year. Promising new developments in cervical cancer treatment, vaccination and improved screening methods will hopefully continue to reduce cervical cancer mortality.

Cervical Cancer Vaccination

Persistent infection with high-risk Human papillomavirus (HPV) causes virtually all cancers of the cervix, most cases of anal cancer and a significant proportion of oropharyngeal, vulval, vaginal and penile cancer. Two vaccines have been developed against HPV infection: a quadrivalent vaccine which targets HPV subtypes 6, 11, 16, and 18, and a bivalent vaccine which target HPV subtypes 16 and 18. HPV subtypes 16 and 18 account for around 70% of cervical cancer.

Two large randomised clinical trials have demonstrated the efficacy of the quadrivalent HPV vaccine, in preventing cervical cancer as well as the pre-cancer, Cervical Intraepithelial Neoplasia (CIN).[1,2] Ninety-seven percent to 100% of females without prior HPV infection were protected against cervical cancer and CIN 2 and 3, while prevention was 44% in women with prior HPV infection. There was also decreased a prevalence of genital warts caused by HPV 6 and 11, and vaginal and vulvar intraepithelial neoplasia.





The efficacy of the bivalent vaccine was similar, shown by a large randomised clinical trial to prevent CIN 2 or 3 as well as cervical cancer in 93% of women.[3]

Comparing the two vaccines revealed that, the bivalent vaccine induced higher titres of antibodies compared to the quadrivalent vaccine.[4] However, it is not known whether the higher serum titres have any impact on the degree and duration of protection. There is currently no defined minimum threshold titre for protection.

The HPV vaccine is most effective among women who have not been infected with HPV, with the optimal time prior to sexual debut. Women who are sexually active, have a history of abnormal Pap smear, genital warts or HPV infection can still be vaccinated. However, HPV immunisation will be less beneficial. HPV immunisation is also not effective in clearing HPV infection that is already present.

The Ministry of Health Expert Committee on immunisation has recommended the inclusion of the HPV vaccines in the National Childhood Immunisation Programme (NCIP) for women between the ages of nine and 26. Clinical trials on the use of HPV vaccination on women older than 26 years old are currently ongoing.

Currently, experimental vaccines are being studied for women with established HPV infections, to help their immune system destroy the virus and cure the infection before a cancer develops. Research is also currently ongoing on vaccines for women who already have advanced cervical cancer that has recurred or metastasised. It is hoped that these vaccines will produce an immune reaction to the parts of the virus (E6 and E7 proteins) that make the cervical cancer cells grow abnormally. This immunity will hopefully kill the cancer cells or stop them from growing.

Vaccination against HPV does not obviate the need for regular cervical cancer screening as there are other oncogenic subtypes of HPV that cause cervical cancer.

Cervical Cancer Screening

Precancerous and cancerous changes in the cervix are commonly detected using the Pap smear test. Current recommendations are for women who are sexually active or who have had sex to go for a Pap smear test once every three years from the age of 25 years.

In HPV-based screening, specimens are collected from the endocervix using a cervical brush, which is then placed in the HPV transport medium. The cell sample is analysed for the presence of HPV. Molecular techniques have shown high sensitivity and reproducibility compared with Pap smears in detecting CIN 2 and CIN 3. It has thus been proposed that HPV-based screening be used both as an adjunct to or in place of Pap smear testing. It can also be used to triage Pap smear results that are equivocal or show low-grade abnormalities.

A pooled analysis of four randomised clinical trials from Europe was recently published in *The Lancet* in November 2013.[5] The study, which pooled more than 175,000 women between the ages of 20 and 64, revealed that HPV-based screening resulted in 60% to 70% better protection against cervical cancer compared to Pap smear testing. The detection of invasive cervical cancer was similar for both screening methods in the first 2.5 years in all four trials. However, after 5.5 years, women whose tests were negative had a higher incidence of invasive cervical cancer than women who were HPV-screened. Women aged 30 to 34 years benefited most from HPV screening. HPV screening every five years was also more protective than a Pap smear every three years.

This study supports HPV-based testing in cervical cancer screening although its role as a population-based routine cervical cancer screening tool in Singapore will require consideration of cost-effectiveness and logistical challenges. At present, guidelines recommend Pap smear screening for women aged 21 to 29 years every three years, with the option of co-testing HPV with Pap smear every five years for women 30 years and older who wish to increase the interval of screening.

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Targeted Therapy

The chance that early stage cervical cancer can be cured is good in most cases. However, the prognosis for advanced stage or recurrent cervical cancer is less optimistic. As researchers learn more about the gene changes in cells that cause cancer, they have been able to develop newer drugs that specifically target these changes. Targeted therapies work by targeting the processes that

control growth, division and spread of cancer cells, as well as the signals that cause cancer cells to die naturally. It is hoped that targeted therapies are able to attack cancer cells while doing less damage to normal cells.

Bevacizumab attaches to a protein called Vascular Endothelial Growth Factor (VEGF), which is required by the body to grow blood vessels. The drug stops tumours from creating new blood vessels to feed the tumour. This limits the tumours' supply of nutrients, which in turn slows or stops their growth. In a phase III randomised clinical trial published in the *New England Journal of Medicine* in February 2014, the addition of bevacizumab to chemotherapy prolonged survival in women in advanced cervical cancer by four months compared to chemotherapy alone.[6] Progression-free survival and response rate was also significantly better. However, the financial costs of therapy will require an extensive discussion with the patient on the balance of the benefits and risks of incorporating bevacizumab into standard chemotherapy treatment.

A phase II clinical study published early in March 2014 revealed that Erlotinib, a drug targeting Epithelial Growth Factor Receptor (EGFR), which is frequently overexpressed in cervical cancer, has shown promise as a new treatment strategy. Erlotinib combined with chemoradiation therapy in women with locally advanced cervical cancer has shown complete response with disappearance of all cancer in 94.4% of women treated. After two years, 91.7% of women were alive, and 80.6% experienced no progression of their disease. We await further confirmatory studies involving larger numbers of patients to establish the role of Erlotinib in cervical cancer treatment.[7]

Other promising targeted drugs being studied include Pazopanib, a drug that blocks the effect of certain growth factors on cancer cells, as well as Lapatinib.

Conclusion

As clinical trials continue to assess new drugs, combinations of chemotherapy, radiotherapy and targeted drugs as well as improve upon methods for screening and prevention of cervical cancer, we look forward to the use of molecular technology and creative new paradigms of treatment to further improve survival and treatment outcomes in cervical cancer. MG

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