

UNIT NO. 5

CERVICAL CANCER PREVENTION

Dr Jeffrey Low Jen Hui

ABSTRACT

The age-standardized rate of cervical cancer in Singapore has fallen from 18.1 per 100,000 between the years 1968-1972 to 10.6 per 100,000 between the years 1998-2002. Its incidence has shown a consistent decline over the last three decades, with the decline in the last 5 years being more marked than before. However, the rates in Singapore continue to be higher than most of Europe and the USA, and lower than parts of Asia, Africa and Latin America. Women not sexually active rarely develop cervical cancer, while sexual activity at an early age with multiple sexual partners is a strong risk factor. About 95% of women with invasive cervical cancer have evidence of HPV infection. Many women with HPV infection, however, never develop cervical cancer; thus this infection is necessary but not sufficient for development of cancer. Measures effective in avoiding HPV infection and thus cervical cancer are abstinence from sexual activity and barrier protection and/or spermicidal gel during sexual intercourse. Risk factors are: cigarette smoking, high parity, oral contraceptive usage among HPV-infected women. Screening via regular gynaecological examinations and Pap test with treatment of precancerous lesions decreases cervical cancer incidence and mortality by more than 80%. Three-yearly Pap testing is effective in reducing the incidence and mortality of cervical cancer. Pap tests have false negative rates of 15-50% and false positive rates of 3-5% for high grade disease - as such, any high grade cytological report must not be dismissed. HPV testing is currently most useful in a woman with ASCUS smear for triaging before colposcopy.

EPIDEMIOLOGY

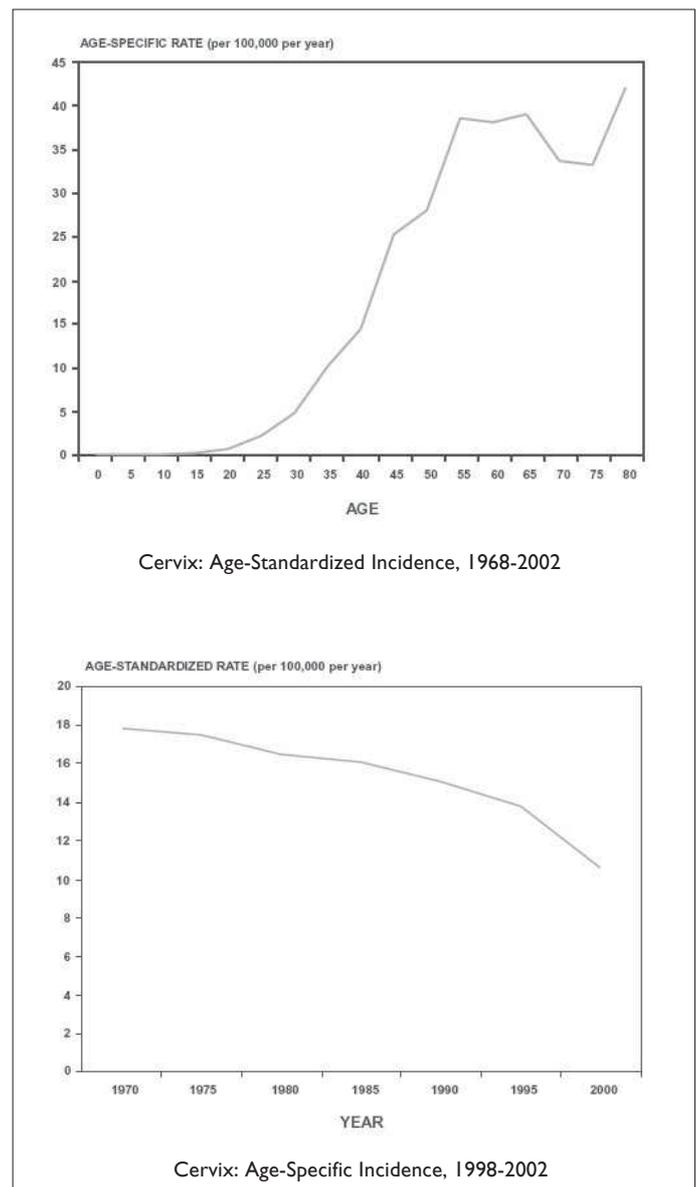
Cervical cancer is the major cause of gynaecological cancer deaths worldwide, with almost half a million new cases diagnosed each year. Reported incidence rates in developing countries are much higher than those in developed countries. The age-standardized rate of cervical cancer in Singapore has fallen from 18.1 per 100,000 between the years 1968-1972 to 10.6 per 100,000 between the years 1998-2002. Its incidence has shown a consistent decline over the last three decades, with the decline in the last 5 years being more marked than before. It has fallen in ranking to fifth commonest cancer among women and second commonest gynaecological cancer in the period 1998-2002. However, the rates in Singapore continue to be higher than most of Europe and the USA, and lower than parts of Asia, Africa and Latin America.

JEFFREY LOW JEN HUI, Head & Senior Consultant,
Gynaecological Oncology Unit KKH

NATURAL HISTORY

Invasive squamous cell carcinoma of the cervix results from the progression of preinvasive precursor lesions called cervical intraepithelial neoplasia (CIN), or dysplasia. CIN is histologically graded into mild dysplasia (CIN 1), moderate dysplasia (CIN 2) and severe dysplasia (CIN 3). Not all of these lesions progress to invasive cancer; many mild and moderate lesions regress. The rate at which invasive cancer develops from CIN is usually slow, measured in years and perhaps decades. This long natural history provides the opportunity for screening to effectively detect this process during the preinvasive phase, thus allowing early treatment and cure. The leading etiologic factor in the development of preinvasive

Figure 1. Cervical cancer in Singapore: age-standardised incidence



and invasive cervical cancer is infection with specific types of human papillomavirus (HPV), transmitted by sexual contact. Thus, women not sexually active rarely develop cervical cancer, while sexual activity at an early age with multiple sexual partners is a strong risk factor. About 95% of women with invasive cervical cancer have evidence of HPV infection. Many women with HPV infection, however, never develop cervical cancer; thus this infection is necessary but not sufficient for development of cancer.

CURRENT EVIDENCE FOR CERVICAL CANCER PREVENTION

The following is a summary of current evidence for cervical cancer prevention:

1. The measures effective in avoiding HPV infection and thus cervical cancer are:
 - a. Abstinence from sexual activity
 - b. Barrier protection and/or spermicidal gel during sexual intercourse
2. Cigarette smoking increases the risk of cervical cancer and precancer by 2-3 times among HPV infected women; passive smoking is also associated with increased risk but to a lesser extent.
3. High parity (7 or more full term pregnancies) is associated with 4 times the risk of squamous cell cancer among HPV-infected women.
4. Oral contraceptive usage for 5-9 years among HPV-infected women have 3 times the incidence of cervical cancer and 4 times when used for more than 10 years.
5. Screening via regular gynaecological examinations and Pap test with treatment of precancerous lesions decreases cervical cancer incidence and mortality by more than 80%.

ROLE OF THE PAP TEST

Cervical cytology screening is, in many respects, the ideal screening test. Cervical cancer has a defined malignant phase of many years, which allows repeated tests to significantly reduce the impact of individual false-negative test results. The Pap test is inexpensive and is readily accepted amongst women. Although never examined in a randomized controlled trial, there is a large body of consistent observational data that supports the effectiveness of the pap test in reducing mortality from cervical cancer. Both incidence and mortality from cervical cancer have sharply decreased in a number of large populations following the introduction of well-run screening programs, in particular, Iceland, Finland, Sweden, USA and Canada. Reductions in incidence and mortality were proportional to the intensity of screening. However the evidence shows that screening every 2-3 years does not increase the risk of cancer above that expected with annual screening.

Nevertheless, the Pap test is by no means perfect. In terms of its sensitivity, false negative rates range from 15-30% for high-grade precancers and up to 50% for invasive cancers (due to obscuring effect of blood and necrotic exudates). False

negative results comprise "true" false negatives (70%) when the slide is free of abnormal cells, and laboratory errors (30%). The main contributing factors to false negative smears are specimen collection, laboratory error and deficiencies in laboratory quality assurance mechanisms. The specificity of the Pap test on the other hand, is quite high at about 95%. With such a low false positive rate, clinicians must be extremely cautious in dismissing an unexplained high-grade cytological report.

REFINEMENTS AND NEWER TECHNOLOGIES IN CERVICAL CANCER SCREENING

In the 1980s, new devices were developed for enhancing the collection of exfoliated cells from the cervix. These include nylon brushes for sampling the endocervix and "broom" sampling devices, which simultaneously sample both the ectocervix and the endocervix.

In an attempt to improve the sensitivity of the Pap test, liquid-based cytology (LBC) has been introduced. In this method samples are collected in the usual manner from the cervix but are then transferred directly into the fixative solution rather than dispersed on a slide. The liquid is then passed through a filter and the cells are transferred to a slide as a monolayer. The slide is then processed like a conventional Pap test. The ability to interpret the slide is improved because the cells are more evenly distributed and there is less artifactual material such as blood and mucus, thus reducing the incidence of unsatisfactory reports. The ability to test LBC specimens for HPV DNA and other sexually transmitted organisms further enhances the clinical appeal of this technology. Although slide evaluation is then performed by cytotechnicians/cytologists, automated image analysis technology may also be used.

Real time screening for cervical cancer using an opto-electronic device called the Truscan consists of applying a probe that analyses its electrical and optical properties of the cervix. This makes it possible to distinguish among normal cervix, precancer and cancer. The potential advantages are instant diagnosis, good acceptance and relatively low cost. This screening method is still being evaluated.

HUMAN PAPILLOMAVIRUS (HPV) DNA TESTING

As virtually all cervical cancers are thought to result from HPV infection, it would be reasonable to consider testing for HPV DNA as a screening tool for cervical cancer. However, there are problems with HPV DNA testing as a primary screening test. The first is to find a feasible test that detects the optimal number of types of HPV that have been associated with cervical cancer. The second problem is that many women have transient HPV infection that is asymptomatic and of little consequence, leading to unnecessary workup. This low specificity of HPV testing is most problematic in younger women who have the highest prevalence of these inconsequential infections.

The ASCUS/LSIL Triage Study (ALTS) found that HPV testing was most useful in triaging women with atypical squamous cells of undetermined significance (ASCUS) findings

on cytologic screening. The study concluded that HPV testing of women with ASCUS smear for triage before colposcopy is a more efficient strategy than immediate colposcopy and also more efficient than conservative repeat-cytology.

Given the etiologic role of HPV in the pathogenesis of cervical cancer, vaccines to immunize against HPV would offer a primary prevention strategy for cervical cancer. A proof-of-principle study of a monovalent HPV vaccine has confirmed a high rate of seroconversion, with none of the vaccinated subjects developing HPV-16 infection or HPV-16 CIN. Promising results from other vaccine trials herald the exciting potential of significantly eradicating cervical cancer in time to come.

CERVICALSCREEN SINGAPORE (CSS)

CervicalScreen Singapore (CSS) is the national cervical cancer screening programme which aims to encourage women aged 25-69 who have ever been sexually active to have pap tests once every 3 years. The guidelines are shown in Table 1.

Table 1. CervicalScreen Singapore Guidelines

1. Entry to Screening Programme	All women who have ever had sex are advised to have their first Pap smear by the age of 25
2. Frequency of Screening	<ul style="list-style-type: none"> Pap smears are taken once every 3 years
3. Discharge from Screening	<ul style="list-style-type: none"> A woman can be discharged from screening at 69 years of age if the smear taken at 69 years is negative and there was a previous negative smear within the last 3 years However if a woman, who has had sexual intercourse, has never had a Pap smear, she should still undergo screening irrespective of her age
4. Women who have never had Sexual Intercourse	<ul style="list-style-type: none"> Women who have never had sexual intercourse need not have Pap smear screening However if these women have any symptoms, they should consult a doctor

Note: Consider screening at an earlier age and at more frequent intervals if high-risk characteristics are present. High-risk characteristics include:

- Multiple sexual partners (either partner)
- Onset of sexual intercourse at an early age
- HPV infection
- History of STD
- HIV infection
- Immunosuppression
- Cigarette smoking

Currently, subsidized screening is available at all polyclinics. A health survey conducted in 2004 showed that 4 in 5 Singaporean women aged 25-69 years knew what a pap smear was and 70% had ever had a pap smear (Table 2). However, only 52% had their pap smear done in the last 3 years. The survey findings revealed that although the knowledge level of pap smear is high, most women are not screened once every 3 years. Under the CSS, letters have been sent to women aged 50-69 years, of which about 10% of these women have gone for a pap smear at the polyclinics. The proportion of women who have gone to private clinics and hospitals for screening is not known.

Table 2. Data from Health Promotion Board (Dec 02 - Sep 05)

1. No. of women screened	58,200
2. Age range	25 - 69 yrs
3. Coverage	52%
4. Abnormal smears	
• ASCUS	1,220 (2.5%)
• Low grade	300 (0.6%)
• High grade	225 (0.5%)
• Cancer	16 (0.5%)
5. Quality assurance issues	<ol style="list-style-type: none"> Unlabelled slides from family doctors sent to labs Incomplete follow-up care of patient i.e. doctors may not track whether their patients go for follow-up at hospitals and what is the assessment outcome

(Source: Health Promotion Board and National Health Survey 2004)

The Health Promotion Board (HPB) has established a quality assurance framework to promote quality standards for Pap smear taking, smear reading and colposcopy. Committees have been established to set and monitor performance standards for key personnel, develop clinical protocols and operational processes for the polyclinics, laboratories and hospitals involved in CSS. The programme has also developed a set of clinical guidelines in a booklet entitled *Management Guidelines for Abnormal Pap Smears and Preinvasive Disease of the Cervix*.

REFERENCES AND RECOMMENDED READING

- MOH. Health Screening. Clinical Practice Guidelines 6/2003. MOH:Singapore.
- Health Promotion Board. CervicalScreen Singapore. Singapore: Management Guidelines for the Abnormal Pap Smear and for Preinvasive Disease of the Cervix. Singapore 2002. URL: http://www.hpb.gov.sg/data/hpb.home/files/pro/cervicalscreen/ManagementGuidelines_PapSmear.pdf
- Seow A. Trends in Cancer Incidence in Singapore 1968-2002. Singapore Cancer Society Report No 6. URL: http://www.hpb.gov.sg/data/hpb.home/files/edu/Report_1968_2002.pdf
- Tay EH. Pap smear screening for cervical cancer in Singapore: issues to consider. Singapore Med J 2004 Vol 45(6) : 244. URL: <http://www.sma.org.sg/smj/4506/4506e1.pdf>
- National Cancer Institute – Cervical Cancer (PDQ®): Screening
- National Cancer Institute – Cervical Cancer (PDQ®): Prevention

LEARNING POINTS

- **Three-yearly Pap testing is effective in reducing the incidence and mortality of cervical cancer.**
- **Pap tests have false negative rates of 15-50% and false positive rates of 3-5% for high grade disease – as such, any high grade cytological report must not be dismissed.**
- **HPV testing is currently most useful in a woman with ASCUS smear for triaging before colposcopy.**