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SPECIAL ARTICLES

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Strategy for cervical cancer screening

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The principle of early detection is based on the assumption that treatment is more effective when the cancer is in pre-clinical early stages. There are 3 approaches to early detection. The first approach is screening asymptomatic populations at regular intervals and further investigation/follow up of screen-positive subjects. With this method, the diagnosis test is used to discriminate high risk from low risk. The second approach is case finding in which refers to detection of early disease in high-risk individuals in opportunistic situations. With this method, the diagnostic test is offered for some purpose and the characteristic of the condition should be known. The last approach is information education campaigns to improve awareness of the general public and to motivate them to seek early detection services. While early detection seems apparently beneficial, it involves substantial costs to the health services and may also result in undesirable side effects. Policy decisions on implementation of early detection procedures for cancer in the health services therefore should consider factors such as the public health importance of the disease, cost-effectiveness of screening and other early detection approaches and the resources available.

The pre-requisites for early detection should be considered. The aim-detected disease should have long pre-clinical phase and curable after treatment. The detection method is suitable, that is, having a high sensitivity and specificity. More than that it should be simple, easily applicable, real time test, rapid, acceptable, inexpensive and non-invasive. The last pre-requisite to be considered is a well-developed health care services, treatment services and follow up applicability.

For early detection of cervical cancer, information education is very important. The effect of education upon the cancer includes the decrease of advanced stage, increase patient's compliance and increase the survival. There are many ways to provide the education. It should be appropriately chosen.

There are many methods for early detection of cervical cancer. They are:

- Downstaging or unaided visual inspection
- VIA
- VIA with magnification
- Speculoscopy
- Visual inspection with Lugol's iodine

- Cytology-monolayer
- HPV testing
- Polarprobe

Considering conventional Pap smears as a screening test, it is agreed that it makes a decrease of advanced stage. However there is some questionable about its performance, now. Performance of conventional cytology in the detection of CIN II and advanced lesion, the false negative rate is between 13-55%. Its sensitivity, specificity, PPV is 44-86% and 90-96% and 18-33% respectively. Too thick smear and severe inflammation cause a difficulty in reading. Monolayer (Thin Prep) can overcomes this limitation. In detection of CIN II and advanced lesion, the Thin Prep has a sensitivity of 86%, specificity of 97% and PPV 31%.

Performance of VIA in the detection of CIN II and advanced lesion, the false positive rate, sensitivity, specificity and PPN is 7-35%, 63-90%, 64-92% and 8-12% respectively. The following data compares the performance of VIA versus VIAM. VIA may be the appropriate method for cervical cancer detection in low-resource settings.

VIA VS. VIAM	Sensitivity (%)	Specificity (%)	PPV*(%)	FNR** (%)
VIA control trial	63	83	9	16
VIAM by midwife	67	85	10	15
VIAM be doctor	80	87	14	19

* Positive predictive value

** False negative rate

The sensitivity of HPV testing in detection of CIN II and advanced lesion is 73-88%, Its specificity, PPV is 81-89% and 18-23% respectively. Because of its cost, it should not be used nationwide programme in developing countries.

Cervical cancer continues to be an important oncological problem in most South East Asian countries and appropriate control measures certainly need attention. Nation-wide screening programmes, in general, are not feasible in almost all South East Asian countries in view of fiscal and technical constraints and the lack of an adequately developed health care infrastructure support screening programmes. In Singapore, where a cervical cytology programme is currently being implemented, efforts should be taken to ensure high quality cytology. Though adjuvant testing with a second test such as HPV testing or VIA may enhance the sensitivity of cytology, it involves additional costs. HPV testing and VIA have proved to be as sensitive as good quality cytology but less specific.

Countries like Thailand and Philippines may consider implementing cervical screening in one or two selected high-risk provinces to begin with and gradually expand the programme later. VIA be considered as a primary screening test in such a programme. The cost of HPV testing is considerable and the available evidence indicates that its sensitivity is similar to that of VIA though it is more specific. Similarly, high investments are required for a good quality cytology programme. Provision of VIA can be integrated in the primary care service. Adequate number of colposcope and treatment (cryotherapy, LEEP) service need to established in the health services in conjunction with the organization of screening. The emphasis should be to provide screening, at least once to women aged 30-54 years.

For other countries, early detection should be through information education campaigns to motivate them for early detection and by building up the necessary human resources and infrastructure in the health services to provide early detection and treatment of pre-clinical lesions. A rough estimate is that one dedicated health worker may be able to examine 7,500 women per year and a colposcopy/treatment (cryotherapy/LEEP) service is required for 600,000 women.

Cervical cancer in South East Asia (SEA)

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The situation analysis of cervical cancer in SEA is very important for cervical cancer control. The population based cancer registry will be substituted the hospital based registry. The incidence from the 5 continents showed that 878600 cancer cases occurred per year. Among these 10% is cervical cancer and it ranks three. This figure however is underestimated.

Most of the cervical cancer occurs in developing countries. It is the second most common cancer in women SEA, and is the most common cancer among women in countries such as Thailand, Myanmar, Laos and Cambodia. In SEA there is 36800 new cases and 206000 deaths per year in the region around 1995. The age-standardized incidence rate of cervical cancer ranged from 6.1/100000 in Hanoi, Vietnam to 25.6/100000 in Chiang Mai, Thailand during 1988-1992. Either the Philippines or Singapore, the age-standardized incidence rate (ASR) is classified as the intermediate rate when compared with the Sub-Sahara Africa. The age-specific incidence rate of the cervical cancer in these two countries are the same, That is steeping upward during 20 years until 50, then plateau. The highest peak is between 50-55 years.

The cancer registries of Bombay, Singapore and Shanghai have been established for a long time. The ASR curve of Bombay and Singapore are similar. They are not decreased too much, compared to Shanghai the incidence is markedly decreased from more than 20 to less than 5. In Singapore the decline of the risk of the cervical cancer has been observed, particularly among the Indian women and to a lesser extent among chines women. However the rates are stable among Malays.

In SEA Indonesia has the highest death rate from cervical cancer, and Brunei has the lowest. Cervical Cancer death rate in Thailand, Singapore and Malaysia are higher than maternal mortality. In Singapore the cervical cancer mortality rates has fallen from 7.3 per 100000 females in 1968-75 to 5.5 in 1983-87. The decrease in incidence in Singapore is comparable with the overall trend elsewhere in Asia, but falls short of that achieved by countries with systematic cytological screening programmes.

Stage of cervical cancer at presentation is a good indicator for cervical cancer control. In Chiang Mai, Thailand, 38% of stage at presentation is localized, compared to 16% in Khon Khean. Five-year survival of cervical cancer in all stages from Chiang Mai and Khon Khaen is 68.2% and 57.5% respectively. The latter is equal to Singapore, whose the 5-year or 10 year-survival is not different too much. Five-year survival of cervical cancer from The Philippines is 29%. It is interested that 5-year survival by clinical stage is very high in Chiang Mai (91%) for localized lesion.

Many independent risk factors for cervical cancer are discussed. The data comes from the case control stage from The Philippines and Thailand. The role of human papilloma virus (HPV) is emphasized. For squamous ell and adenocarcinoma cervical cancer, the odd atio is 156, and 111 respectively for HPV positive cases.

Concerned efforts at health education and early detection linked with treatment are likely to further reduce the risk of and mortality from cervical cancer in the region.

Appropriate strategy for cervical cancer screening in South East Asia countries

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Thailand has an area of 513,155 square kilometers. It is divided into 76 provinces, with four geographic regions: the northern, northeastern, southern and central. The total population is about 60 millions. The proportion aged 15-59 was 72% and 6% for age 60 and over. The person per hospital bed is 666. The doctor per persons is 1:4,260. Specialized treatment for cancer has been provided by the oncological units in the major teaching hospital around the country and the National Cancer Institute in Bangkok. Since 1989, six regional cancer center have been established as well as the cancer registry in the different parts of the country.

During the last 20 years, the leading cause of death in Thailand has changed from infectious disease to non-communiable disease such as heart disease, malignant neoplasms, accidents and poisonings. Among these, the deaths for all types of cancer in female are 27.6 per 100,000 (crude rate) and 39.2 per 100,000 (ASR). Uterine cancer, which included both cervix and corpus is the most common site of cancer death in female.

Although the first leading female cancer is different in each part of the country, cervical cancer is still the leading female cancer in Thailand followed by breast and liver respectively. The ASR of cervix during 1992-1994 is 20.9 and there are almost 5,500 new cases of cervical cancer per years. The age specific incidence curve show a pattern of early, that is staring before age 20, with a steep rise to about age 45-60, followed by a plateau and decline. Squamous cell carcinoma is the most common (80-86%) with adenocarcinoma accounting for 12-19%. The stage at diagnosis is often advanced and overall 5 years survival is about 60%.

The hospital-based data, case-control study of invasive cervical cancer in Thailand showed that HPV DNA was detected in 95% of patients with squamous cell carcinoma, 90% of those with adenocarcinoma/adenosquamous carcinoma and 16% of control subjects. For patients with squamous cell carcinoma, the most common types of BPV found were type 16, 18, 58, 52 and type 31 respectively. For patients with adenocarcinoma/adenosquamous carcinoma, the most common HPV types found were type 18, 16 and type 45. The risk factors that remained associated with risk of both histological types are adjustment for HPV and their mutual confounding effect were limited education, increasing number of sexual partners, history of venereal diseases and interval since last Pap smears test. Among patients with squamous cell carcinoma, some association with smoking was also observed. In 1999 there is a consensus of the 5-year National Planning for Prevention and Control of the malignant neoplasms. The goal of the National policy for cervical screening is decreasing a half of the incidence and mortality of cervical cancer in 5 years. The policy aims to perform the Papanicolaou smears in the women aged 35-54 years, who have never been screening for the last 5 years ago and the interval of screening is every 5 years. Because the total target population is 10 million, the 50% coverage is 1 million per year. The government will support organized screening programme as a mean for reaching a high proportion of ate at risk population. Quality control systems for the screening tests and defined mechanism for referral and treatment of abnormality will be put in places. The major activities during 5 years include nationwide Pap smears screening, as well as the essential system for screening, such as interpretation and reporting system, pre-invasive treatment system, evaluation and monitoring system. The estimated total budget which the cost for diagnosis and treatment of the invasive stage are excluded is 923 million bath. Most of the budget will be spent on interpretation and reporting system.

The demonstration programme of cervical cancer screening launched by the National Cancer Institute of Thailand uses the Pap smear as the principal screening test, backed up by colposcope. The main Treatment methods for pre-invasive lesion are LEEP and cryotherapy. The facilities of the primary health care team will be employed in implementing screening. The results of the participation and compliance with screening will be the indicator of success. This project has a hopeful of improving the quality cervical cytology in the country and lead to manpower development in areas of smear taking, cytology, colposcopy and management of pre-invasive lesions.

Nowadays there are many ways to improve cervical cancer screening. Liquid-based cytology, HPV DNA testing, Polarprobe, spectroscopic techniques, are the example of these. In Thailand, none are available, the main method for screening in this Kingdom is solely conventional cytology. A self-administered device for cervical cancer screening, VIA and Fourier Transform Infrared Spectrometer are experimental technologies used in Thailand at the present time. Among these, VIA is the most promising.

The SWOT analysis of cervical cancer control situation in Thailand show that. The strength is well-established tumor registry and a strong primary health care team. The weakness is lacking of effective National policy, well-organized treatment strategy and resources to initiate a comprehensive screening and treatment programme. The opportunity is having an established 6 regional cancer center and external fund to support appropriated screening method. However the threat is a long period economic crisis and instability of government policy.

From the many points of view described above, to control the cervical cancer in Thailand, Provision for a screening policy should be implemented as soon as possible. Pap smears should still be used as a screening method. A central coordinating unit should established for responding the quality control of the cytology, a network for referral and management the pre-invasive stage and monitoring the activities of the programme. If this can not be urgently done, cervical is still be a great murderer for the Thai women, and this country will be the example of having a good intent but having none of effective action to control this cancer.

Colposcopy in cervical cancer screening cervical cancer and HPV

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In United Kingdom, the coverage rate of Pap smears is 85%. Colposcopy is the method for the visualization of the cervical epithelium. Specific features characterize low and high-grade epithelial neoplastic conditions i.e. CIN. Colposcopy can therefore be used in a screening method under 2 conditions.

1. As a population screen in those populations in whom cervical cytology is of questionable quality. In those countries in which screening for cervical neoplasia is done by colposcopy, the technique shows a high sensitivity but very low specificity. It is also traditional for cervical cytology to be used in conjunction with colposcopy, and the fusion of both these techniques improves the specificity and increases the sensitivity. With the introduction of HPV DNA testing of oncogenic types, it has been showed that primary cervical cancer screening would be modified and significantly improves by introducing HPV testing alongside colposcopy and cytology. Where colposcopy has been compared to HPV DNA test it was always found to be less sensitivity.

The data from the American ALTS study which was randomized multi-center clinical trial comparing three management strategies with women referred with cytological diagnosis of low grade smears, confirmed the efficiency of HPV DNA testing compared to cytology and colposcopy. In a recent German study by Schneider et al., the sensitivity of cytology and colposcopy under screening conditions was shown to be low in middle aged women. However the negativity for oncogenic HPV types was associated with every low prevalence of CIN II or III or cancer. Schneider and his group felt that testing for oncogenic types was more efficient than cytology and colposcopy and also would allow an increase in the interval for screening of the cervical cancer. Oftener and his group likewise have compared primary screening in German with Pap smears was inadequate protection and that a more sensitive technique resided in HPV testing.

2. As a referral system in those women who have already been detected as having abnormal cervical cytology, and/or positive HPV DNA testing.

Once a women has been detected as having an abnormal cytology or HPV positivity for oncogenic types colposcopic screening becomes routine. In many units the development of an ASCUS border smear on at least 3 occasions over an 18-month period would be grounds for colposcopic referral. This seemingly lengthy period of delay takes into account the high progression rate of these lesions.

Possession of a mild or LSIL smears six months apart, is further indication for colposcopy. A referral for colposcopy is essential for one high-grade smear (HSIL).

With the introduction of testing for HPV DNA to detect high-grade oncogenic types, the criteria for colposcopic referral have been enlarged. Women under the age of 30-32 with positive HPV oncogenic types are seen at the end of 6 months later and if the positivity still remains, the colposcopic referral is initiated. Women over the age of

32 are referral on just one such positivity result. This reflects the evidence that in women under 30-32, high rates of regression occur and one positive result most likely indicates transient disease. However, over that age, the findings indicate most likely persistent disease and a high risk of the presence of high-grade pre-cancer of its subsequent development.

In summary, the indications for colposcopy referral age

- moderate, severe dyskaryosis
- glandular abnormality
- mild dyskaryosis in poor compliance cases
- after conservative treatment
- suspect of invasive lesion
- inadequate or borderline Pap smears
- micro-invasive lesion (squamous or glandular cells)

The conditions that colposcopy may be replaced are as the following

- Triage of methods in equivocal smears; ASCUS, AGUS or LSIL
- In women with inadequate smears
- Follow-up after treatment of CIN

Immediate colposcopy gives an accurate CIN diagnosis, an decrease of CIN progression and detection of missed disease from cytology.

The colposcopic examination provides information regarding the type of epithelial lesion and a grade system has been developed by Reid et al. Basic colposcopic criteria will differentiate in most cases low grade from high-grade disease by this scoring system.

During colposcopic examination, if there is a large high-grade lesion, beware of micro-invasive lesion. There is a relation between severity and the number of CIN III present in conization specimen. Glandular cervical cancer is about 4-5%. Adenocarcinoma in situ (AIS) detection is difficult in lesion lies beneath the surface of epithelium. The AIS is usually a focal lesion, 15 mm or less in size. The ratio of AIS and HSIL is 1.5 mm atypical AIS or glandular lesion are shown as the big gland, big mouth and reddish.

There are 2 techniques that will challenge colposcopy are HPV DNA testing and real time electronic detection. Other adjunctive techniques are direct visual inspection, speculoscopy, polarprobe and cervicography.

Treatment of pre-invasive cervical lesion

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In dealing with the pre-invasive cervical lesion, the following triage rules should be emphasized.

1. Invasive cervical cancer at T-zone has to be excluded, endocervical canal has to be assessed
2. Histological diagnosis is made by target biopsy
3. Diagnostic conization reserves for micro-invasive cervical cancer

Historically, hysterectomy was considered to be the definitive treatment for pre-invasive cervical lesions. It has been shown that recurrence of pre-invasive and subsequent invasive cancers, are as common after hysterectomy as after conization, so conservative treatment is now the norm.

There are many methods of conservative treatment for -pre-invasive cervical lesions available including cold knife cone biopsy, radical electrocoagulation diathermy, laser ablation, laser cone, cryotherapy and large loop excision of the transformation zone. For small low-grade lesions, all are equally effective, but not all are as effective for larger, higher-grade lesions.

The principle of conization composes of excision of T-zone, getting an adequate margin, endocervical curettage and geometry tailored to lesion. The indications of conization are CIN III, suspected invasive lesion and pathological diagnosis of micro-invasive cancer. The complications of conization are acute bleeding, infection, delayed cervical stenosis and infertility. The incidence of primary and secondary hemorrhage is 6% and 7% respectively. The incidence of cervical stenosis is 17%, among these half has symptoms. The cone dimension should be more than 25 mm in depth and base width. The benefit of cold knife conization is that, it is an easy basic surgical skill and obtains a clear margin. The laser conization is more expensive, however laser can cause less bleeding than cold knife conization.

The electrocautery treatment of CIN yields a high primary cure rate because it can eradicate the extensive and deep area at the cervix and distal endocervical canal. It is also an easy and quick method as well as painless and well tolerated. This method requires anesthesia. Vaginal discharge due to infection, bleeding and stenosis of the cervix can occur. However the major disadvantage of this method is inaccessible of squamocolumnar junction.

Laser vaporization of CIN requires anesthesia. The ablative technique should be performed to obtain 7 mm in depth and 12 mm at the central base. The rule of laser vaporization is that, the invasive cancer should be ruled out before laser ablation is done. The follow-up assessment is mandatory. The complications of this method are bleeding and cervical stenosis. The overall success rate is 96-100%. In CIN the success rate is 98% while CIN II, III has success rate about 95% or more.

The LEEP technique is appropriate for all patients triaged to T-zone ablation or excision. These patients have an abnormal cytology and colposcopic lesion diagnosis. When compare to laser ablation. It is more easy and quick, require only local anesthesia, able to do in the office, less bleeding and less expensive. More than that, it obtain tissue for pathological examination. Thus invasive disease and adenocarcinoma can be detected. The complication of LEEP is primary and secondary bleeding. Factors that influence to LEEP failure rate are incomplete destruction, glandular lesion, unfavorable healing and Koebner phenomenon.

Cryotherapy is an out patient procedure, which requires none of anesthesia. The important things of this technique

are probe position onto tissue and freezing until ice ball developed 5 mm beyond the edge. The persistence of disease after double freeze technique is 8.8%, after single freeze technique is 27.5%. The persistence of disease correlate with severity of CIN and number of quadrant that has a disease.

In general, selection the method of treatment will depend on the natural disease, diagnosis confidence, fertility issue, availability, cost effectiveness and morbidity. In addition to the effectiveness of the methods, the cost of equipment, the type of anesthesia needs and the amount of technical skill involved in performing the treatment are important consideration, particularly in developing countries.

The speaker favors large loop excision of the transformation zone using local anesthesia as the treatment of choice in developing countries on the grounds of simplicity and cost effectiveness.