

The cervical smear test in the next millennium

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This paper traces the cervical Papanicolaou smear test from the seminal work of George Papanicolaou undertaken more than 70 years ago, to the present use of computer technology to examine cervical smears. However, to successfully detect cervical cancer and precursor lesions, the standard of the specimens, as well as that of the screening laboratory, must be of the highest order so that false negative results are eliminated. Newer sampling devices, techniques for improving specimen quality, computerised laboratory technology, and the need for laboratory accreditation are also discussed. The Papanicolaou test is the most successful test invented for cancer prevention but despite this, up to two thirds of Hong Kong women have not had a test. There is a need for increased public health education directed at women so that there is a greater awareness of the importance of disease prevention, with an emphasis on cancer prevention. The implementation of a cervical screening programme in the new millennium will ensure that women receive all the benefits that the Papanicolaou smear test can confer.

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Introduction

The cervical smear test was devised more than 70 years ago and has helped to substantially reduce the incidence of cervical cancer. In Hong Kong, however, the effect of the test has been limited, and cervical cancer remains a significant disease, being the fourth most common cancer in women.¹ This is not surprising, as the majority of Hong Kong women have not had a cervical smear.^{2,3} This is most unfortunate, as the Papanicolaou (Pap) smear is one of the most effective tests invented to prevent cancer. It has been said that "with the exception of stopping the population from smoking, cervical cytological screening offers the only major proved public health measure for significantly reducing the burden of cancer today."⁴ Others have placed the Pap test alongside other great medical triumphs such as the vaccines for smallpox and polio.⁵

Most cervical cancers have a long pre-invasive stage that can be readily detected with a well-taken

Pap smear. By giving appropriate treatment, future cervical cancer is prevented from developing. In contrast, fully developed cervical cancer is an aggressive disease and, even with modern treatment, achieving a cure can be difficult. There are very few cancers that can be easily detected at a pre-invasive phase. For example, the two leading malignancies in Hong Kong women—lung and breast cancer¹—are exceedingly difficult to diagnose in the early stage of disease, even when the latest technology is used. Striving for the early diagnosis of any cancer is important, as this will ensure optimal prognosis after treatment.

Development of the cervical smear test

While investigating hormone-associated changes in cells that were present in secretions obtained from the upper vagina, Papanicolaou identified cancer cells in some of the samples. The cells had exfoliated from the cervix and had then accumulated in the upper vagina. In 1928, he presented his findings at an international meeting but there was little interest in his results.^{6,7} Papanicolaou continued his research and in the early 1940s, co-published a landmark paper and a monograph that described the cytological diagnosis of uterine cancer by using vaginal smears.^{8,9} Despite having a lesion in the cervix, many women whom he studied showed no clinical evidence of disease. This

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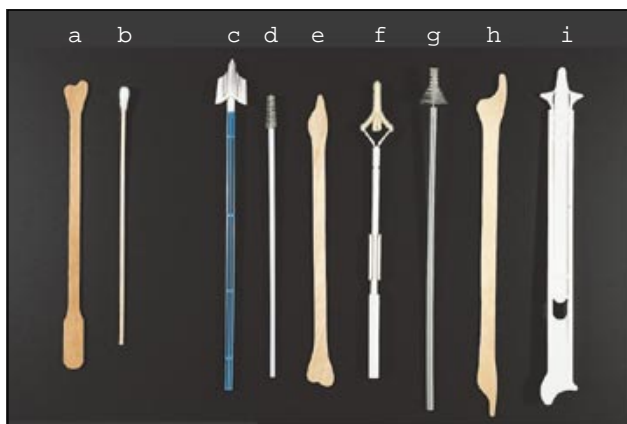


Fig 1. Various cervical smear sampling devices (a) original Ayre spatula; (b) cotton-tipped applicator; (c) Cervex brush; (d) Cytobrush; (e) modified Ayre spatula (widely used in Hong Kong); (f) Acellon Combi biosampler; (g) and (i) plastic devices for obtaining ectocervical and endocervical samples; (h) Aylesbury spatula

is a particularly important observation, because most pre-invasive cervical lesions are not only asymptomatic, but also invisible to the unaided eye.¹⁰

The use of cytology to diagnose cancer was enthusiastically welcomed by gynaecologists. After the method had been confirmed to be reliable at detecting both cancers and pre-invasive lesions, it was rapidly put to clinical use.⁷ In 1947, the Canadian gynaecologist Ernest Ayre described the use of a purpose-designed wooden spatula to directly scrape cells from the surface of the cervix for microscopic examination.¹¹ Prior to this, material had been aspirated from the upper vagina. Ayre's method for obtaining a Pap smear sample remains unchanged today: the spatula that he designed is still widely used and has been only slightly modified (Fig 1), and most cervical smears in Hong Kong are obtained using this device.¹²

Cervical cancer is a global disease

Cervical cancer is an important cause of malignancy in women and worldwide each year, there are around half a million new cases and more than 200 000 deaths as a result of it.^{13,14} In Hong Kong, there are about 500 new cases diagnosed annually, and approximately 150 women die from the cancer.¹ In 1995, there were 159 cervical cancer deaths; of the women who died, 35 (22.0%) were younger than 50 years and two (1.3%) were in the age-group of 20 to 29 years. In the same year, there were 2599 admissions to government and private hospitals for cervical cancer, which would have involved substantial expenditure.¹⁵

The incidence of cervical cancer is very low in countries that have good Pap smear screening coverage. In

three Scandinavian countries—Finland, Sweden, and Iceland—the number of cervical cancer cases fell by 50% and associated deaths decreased sharply after comprehensive Pap smear testing was introduced.^{16,17} Similar dramatic reductions occurred in North America when Pap testing was widely used. In British Columbia, Canada, the number of cases of cervical cancer decreased by 85% between 1955 and 1984¹⁸ and in the United States, the incidence of cervical cancer fell by 70% after screening started.^{19,20} In Hong Kong, there has been no significant reduction in the mortality rate and incidence of the cancer¹ and the percentage of women who have received a smear test is estimated to be very low. Local studies suggest only one third of women have been tested.^{2,3} This is an unacceptably low figure for a rich community, which has a modern health care system. Studies show that women who continue to develop cervical cancer are those who have never had a Pap test or have been infrequently tested.^{21,22} Consequently, in developing countries, where screening programmes are non-existent, cervical cancer is the most common female malignancy.^{13,14}

The 'Pap' smear test at the crossroads

Although it is an effective test, the Pap smear's role in cervical cancer prevention will not advance any further in Hong Kong unless two issues are addressed. Firstly, plans need to be devised to ensure the large number of women who have not been tested are screened. Secondly, improvements need to occur in the quality of the Pap smear specimen collected and the laboratory standards used in the assessment of the smear.

Improving the quality of the test specimen

The ability of the Pap smear to detect a lesion is greatly influenced by the quality of the specimen.

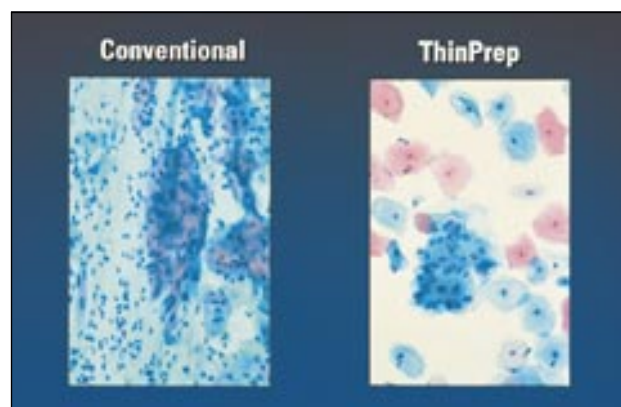


Fig 2. A comparison of a thin-layer (ThinPrep) Papanicolaou smear and a conventional smear. The thin-layer smear (right) has a clean background, which makes the examination quicker (Papanicolaou stain, x100)

Even when the most advanced technology is used in the laboratory to examine smears, a lesion will remain undetected if the smear is of inferior quality. A good Pap smear contains endocervical and/or metaplastic cells; their presence indicates that the 'transformation zone', where most cervical cancers originate, has been adequately sampled. Studies have shown that women whose test results had been 'normal' and then who subsequently develop cervical cancer, had smear specimens that did not contain any endocervical cells.²³ Laboratories have a responsibility to indicate the adequacy of a Pap smear in their report and to request a further smear if a suboptimal one has been provided; fulfilling this responsibility would ensure that women have an adequate test performed. In the widely used Bethesda System for reporting Pap smears, specimen adequacy is stated in the report.²⁴

New cervical cell samplers

The Ayre spatula, when used alone, may not produce an adequate specimen, as many cells are not transferred onto the glass slide and are discarded with the sampling spatula.²⁵ Consequently, cells that are necessary for the diagnosis may be absent, thus resulting in a false negative assessment. New sampling devices have been devised to improve specimen quality. Two that are available in Hong Kong are the Cytobrush (Medscand, Malmo, Sweden) and Cervex brush (Rovers B.V., Oss, The Netherlands) (Fig 1). An adequate specimen can be obtained by using the modified Ayre spatula to collect an ectocervical sample and a Cytobrush to obtain an endocervical one. The two samples can be placed on the same slide,²⁶ but for ease of handling, clinicians tend to use a separate slide for the two samples. This results in two slides being produced and increases laboratory workloads substantially. The Cervex brush was designed to produce a comparable sample to that obtained by using both a wooden scraper and a Cytobrush and has been shown to be an effective instrument.¹²

The advantages of preparing thin-layer smears

A major problem with Pap smears is the development of drying changes in cells due to a delay in applying the spray fixative or immersing the slide in 95% ethanol.²⁶ Smears that have dried by air are very difficult to evaluate, and any abnormal cells present may not be identified.

The thin-layer method has been used successfully to prepare non-gynaecological specimens; when used to modify Pap smear-taking, the thin-layer method

eliminated the drying problem.^{25,27,28} The thin-layer smears are collected in the usual manner with a non-absorbent instrument such as the Cervex brush. Instead of being smeared onto glass slides, however, the cells are rinsed into an alcohol-based solution. The thin-layer technique not only eliminates drying changes, but also speeds up microscopic examination because blood, mucous, and inflammatory cells are removed during processing (Fig 2). In addition, the cells are deposited in a thin-layer located within a circle, which ranges from 13 to 20 mm in diameter. In a conventional smear, the cells can be located anywhere in a much larger rectangular area measuring 50 x 20 mm. The two thin-layer processors currently available are the AutoCyte PREP (Autocyte, Burlington [NC], United States) and ThinPrep Pap Test (Cytic Corp., Boxborough [Mass], United States).

Only an aliquot of cells is used for each thin-layer smear but despite this small volume, sufficient cells are present to allow an abnormality to be detected. The phenomenon of 'random subsampling' applies when cells are uniformly mixed and distributed in the liquid fixative. Consequently, there is an equal likelihood of diagnostic cells being deposited on any given slide.²⁷ In split-sample trials, a conventional smear specimen is first placed onto a slide and the sampling device (that contains residual cells) is then rinsed in a fixative and thin-layer slides are prepared. When multiple slides are prepared from one cell suspension, diagnostic cells can be detected in up to 10 thin-layer samples.²⁵ Studies show that the detection rate matches conventional smears for benign cellular changes, but for the detection of squamous intraepithelial lesions and cancers, the thin-layer method is superior.²⁸ In addition, unsatisfactory smears are encountered less often.²⁹ As the cells in the liquid medium are stable for many weeks, ancillary tests such as the detection of human papillomaviruses (some subtypes of which are strongly linked to cervical cancer) can be performed.³⁰

Pathologists and technologists need to receive retraining in the interpretation of cellular changes in thin-layer Pap smears, as the cellular changes differ from those found in conventional smears.²⁷ Another drawback is the cost involved in preparing each thin-layer Pap smear. The additional costs are for the non-absorbent sampler, liquid fixative, special slides, filters, and the substantial outlay for the thin-layer processor. In an Australian study,²⁹ patients were levied an additional fee of A\$20.30 (HK\$101.50) if they requested a ThinPrep Pap smear. In the United States, the additional cost has been estimated to add US\$10.00

(HK\$78.00) to each smear.³¹ The extra cost will have to be borne by the laboratory, the patient, or by health insurance organisations. Costs may drop when robotic equipment that can process multiple samples simultaneously becomes available.

Laboratory standards in the United States

In the United States, articles that appeared in the *Wall Street Journal* in 1987 led to major improvements in laboratory standards and hastened the development and employment of new technology.^{7,19} The articles revealed that some commercial laboratories had low operating standards and paid staff according to the number of Pap smears they examined daily, thereby encouraging technologists to examine excessive numbers of smears. In addition, work was often undertaken at home and there was a lack of adequate supervision. This shoddy work practice resulted in an unacceptably high false-negative rate. The revelations created a public uproar and resulted in congressional hearings, the revision of the existing laboratory regulations, and the enactment of the Clinical Laboratories Improvement Amendments act of 1988. The revised regulations laid down guidelines on the maximum number of slides to be screened daily by a technologist and required that all abnormal smears be examined by a pathologist before a report is issued. In addition, laboratories were ordered to rescreen 10% of their negative Pap smear results. The monitoring of cytopathologists and cytotechnologists was assigned to the Centers for Disease Control and Prevention in Atlanta. These stringent regulations resulted in the disappearance of many substandard laboratories.^{19,32}

The general public became more aware of the importance of laboratory standards and the value of the Pap test. Unfortunately, there was also an unrealistic expectation that the Pap smear was a totally accurate test. It was wrongly assumed that a false negative result was solely due to laboratory negligence and, regrettably, this has resulted in many lawsuits.³³⁻³⁵ One quarter of all pathology-related lawsuits are related to the Pap smear.³² Because of the fear of litigation, some laboratories no longer examine Pap smears.³³

Local matters

In Hong Kong, there are no regulations governing the examination of Pap smears. In establishing a private medical laboratory, the only requirement that must be met is its registration as a business.³⁶ From personal knowledge, it can be said that cytology laboratories in Hong Kong have standards that range from the very

high to the very poor. In 1994, a medical bulletin report described the practice of private laboratories hiring government laboratory personnel who were already “tired from reading slides all day” to work after hours and also mentioned medical technologists “moonlighting” in “back-street laboratories.”³⁶ Under such adverse conditions, it would be hard to achieve a high standard of Pap smear reading. However, there are still deficiencies even in the laboratories that are well equipped, have appropriately qualified staff, undertake regular quality assurance exercises, and generally strive for a high standard of work. Unfortunately, there are no local statutory requirements for the periodic inspection of laboratories by an independent body for accreditation and licensing purposes.

Laboratory accreditation

Contemporary medical practice requires laboratories to be able to produce results that are accurate. When a laboratory is accredited, it indicates that a structural mechanism is in place, which allows high-quality laboratory work to proceed, and that the workplace is safe for staff. “Do not send out a test result (report) that you would be unwilling to have used in the diagnosis (treatment) of your own illness”³⁷ is a statement that sums up what laboratories should be striving for. Yet, at the time of writing, no Hong Kong medical laboratory—government-funded or private—has been accredited by a recognised laboratory accreditation agency similar to the National Association of Testing Authorities, Australia or the College of American Pathologists.

To pass an accreditation inspection, all aspects of laboratory activity are scrutinised. The way in which tests are performed, staff qualifications and experience, methodology, reporting practice, record-keeping, and quality-control programmes (both internal and external, staff training, continuing medical education, and safety) are considered. Hong Kong has a poor record for safety and this is also the case with medical laboratories in which staff daily encounter dangerous chemicals and potentially infectious specimens. Laboratory administrators should ensure that the handling of specimens and chemicals, and the operation of equipment conform to internationally accepted standards. Unfortunately, relying solely on staff members’ conscience or sense of moral obligation is not sufficient to guarantee safety in the workplace. Statutory regulations that are strictly enforced are also needed to guarantee that staff are not exposed to danger. An important component of any safety programme is staff training, so that a ‘safety culture’ is

instilled and eventually becomes the benchmark for behaviour. Some additional benefits from successful accreditation include industry recognition that an organisation is quality-focused, the increased opportunity of collaborative work, and the facilitation of securing research funding. Laboratory staff will also feel an enormous sense of pride and achievement, which can engender greater teamwork and encourage further improvement in the workplace.

In many countries, accreditation is mandatory, and repeated failure to achieve this can lead to the withdrawal of funding or even the closure of the laboratory. Poor laboratory standards can have catastrophic consequences for patients and should be the overriding factor in deciding whether or not accreditation is sought. The fact that the exercise will cost money should not be a consideration. The recent spate of Hong Kong medical blunders that have been widely reported in the media should be a signal for laboratories to look at ways of ensuring high standards are maintained so that the potential for mistakes is minimised. Accordingly, laboratory accreditation and licensing should be seriously considered.

Computer technology in the laboratory

The examination process of Pap smears is very labour-intensive; various human factors can lead to errors, the most serious of which is the false negative report. As the abnormal cells have been 'missed' by the reporting laboratory, a lesion will remain undetected. False positive results, while not as serious, can lead to unnecessary patient anxiety and treatment.

Helper computers

To improve human screening, 'helper' computers can be used. Such a system—the PathFinder system (Neopath Inc., Redmond [Wash], United States)—was recently installed in the Cytology Laboratory of the Prince of Wales Hospital.³⁸⁻⁴⁰ This system comprises a number of workstations, each consisting of a micro-computer and a 5-inch monitor that is linked to a conventional microscope that has a position sensor attached to the stage (Fig 3). When the Pap smear slide is examined, the *x-y* coordinates of the slide are displayed as a 'map' on the monitor (Fig 4). A series of small solid circles indicates a momentary pause as a screener evaluates a cell or cell group and the map can tell the observer which areas have been screened and which have been overlooked, so that remedial action can be taken. An electronic tagging and labeling system allows abnormal cells to be marked. This



Fig 3. A cytotechnologist using the PathFinder helper computer at the Prince of Wales Hospital

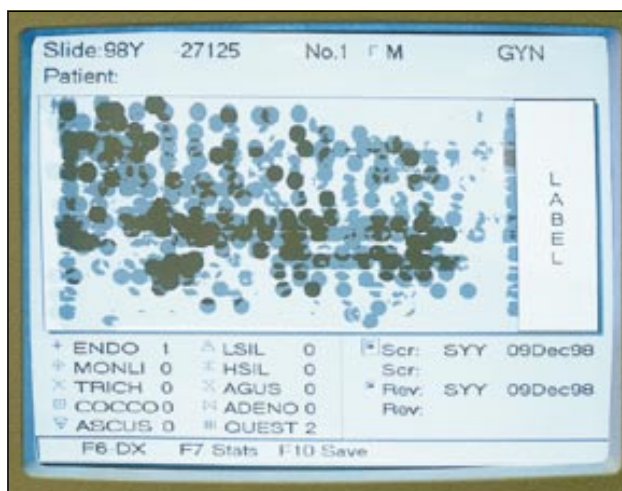


Fig 4. PathFinder monitor showing the 'map' of a Papanicolaou smear that is being examined. The small circles indicate a momentary pause as a screener evaluates a cell or cell group.

information and the screening 'map' can be stored in 90-mm computer diskettes and retrieved for review. The marking system eliminates the need to use marker pens to identify abnormal cells, which is the current practice in laboratories. In addition, a number of workstations can be linked to a server and a record of work undertaken by each screener can be recorded, thus allowing workload statistics to be gathered easily. The system can also be used for quality assurance functions such as the correlation of previous smear results with the relevant biopsy results. The system can also be used to generate Pap smear reports.

Studies have indicated that productivity can be improved by 15% with the use of these computers.^{37,38} This system can have a significant impact on the output and accuracy of a cytology laboratory.

Automated screening

When a person examines a Pap smear with a microscope, an entire cell or field can be evaluated and a decision can be quickly made as to the nature of the cellular changes. However, for this to be done by a computer screening instrument requires extremely sophisticated computer technology. The instrument needs to be able to recognise normal and abnormal cells as well as blood cells, debris, and other constituents present in a Pap smear. In recent years, instruments have been developed that are able to examine Pap smears.^{27,39} Such processors have been extensively tested and two instruments have been approved by the United States Federal Drug Administration for clinical use. Both instruments are available in Hong Kong. The PapNet (Neuromedical Systems Inc., Suffern [NY], United States) is used to recheck slides

5a.



5b.



Fig 5. The AutoPap primary screening instrument at the Prince of Wales Hospital (5a) a technician loads trays of cervical smears to be processed; (5b) trays of cervical smear specimens

that have already been manually screened and the AutoPap (NeoPath Inc., Redmond [Wash], United States) is a primary screening instrument (Fig 5). The AutoPap device is located in individual laboratories whereas the PapNet is located in a regional centre to which slides must be shipped for their evaluation.²⁷ These automated screening instruments still require human input, but in the case of the AutoPap system, a proportion of Pap smears need no human evaluation, thus eliminating tedious repetitive work and saving manpower. The use of automated screening instruments has further improved lesion detection rates.²⁸

Computerised screening instruments

The following minimal requirements should be met if computer screening is to have any practical value³⁹:

- (1) The sensitivity should equal or better that of the conventional methods;
- (2) The specificity should be high, so that the system is cost-effective;
- (3) Inadequate specimens should be identifiable;
- (4) All abnormal specimens should be detected;
- (5) Abnormal samples should be identified and marked for later human review;
- (6) The time taken to screen a smear should be reasonable; and
- (7) The cost should be no more than that of a conventional examination.

Automated screening instruments can operate continuously and undertake repetitive work, thus enabling skilled (and high-salaried) staff to perform other tasks. However, the most important attributes of any instrument are the ability to reduce false negative smear results and to increase the rate of lesion detection. It is also important to have a zero false-positive rate so that money and resources are not wasted on unnecessary investigations and treatment.

Primary screening instruments may have an important role in developing countries, which have a shortage of skilled pathologists and technical staff, and where cervical cancer is a major problem.³⁹ The goal of having less human involvement in the examination of Pap smears is slowly being realised and in the next millennium, there will undoubtedly be some very innovative technological developments.

A case for prevention

Treating cancer is not only expensive but cure is often not possible and invariably there are other 'costs', which can exert a heavy burden on the patient,

family, and community. The goal of increased cancer prevention should be vigorously championed by both the medical profession and the government. A well-researched report concluded that despite many decades of concerted basic research, and multitudes of treatments being tried, cancer remains undefeated and that the only hope for changing this was "a commitment to the prevention of cancer."⁴¹ The exceedingly low Pap smear coverage in Hong Kong is compelling evidence of a lack of commitment to prevention by the medical profession and the government. A 1998 report by the Hong Kong Council of Social Services on estate doctors showed that only 9.3% of patients surveyed were advised by their physician to have a regular check-up.⁴² Convincing more women to have Pap smears is a formidable challenge and will require the formulation of a screening policy and the implementation of appropriate strategies.

Hong Kong needs to institute a cervical cancer screening programme

To reduce the incidence of cervical cancer, women who have either not had a smear or been infrequently tested need to be targeted and given the opportunity to have regular tests. To accomplish this aim, the medical profession and the government will need to work closely together. There will need to be appropriate education and publicity, the setting up of a Pap smear screening registry, adequate laboratory services available, and provision made for the treatment and management of women with abnormal Pap smear results. For such a scheme to succeed, there will need to be sufficient funding. A joint government and private medical practitioner scheme is one way to proceed. In many countries, private family physicians are the key to successful Pap smear programmes and a government subsidy can be an incentive for private doctors to participate. The use of personnel other than doctors may need to be looked at to ensure that adequate smears are taken.

A role for nurses

Studies from overseas have shown that well-trained nurses are capable of taking Pap smears⁴³ and being of the same sex can also be a distinct advantage with certain ethnic groups.⁴⁴ In a report from the United States, nurses who had only 1 week of training produced excellent-quality smears.⁴⁵ One study⁴⁴ has shown that some doctors view the participation of nurses in smear-taking as a threat and erosion of their role and authority. Some doctors stated a routine bimanual pelvic examination was an important part of

the cervical smear examination and this was a reason why only doctors should take Pap smears.⁴⁴ There is, however, little evidence to indicate that a pelvic examination is effective in detecting endometrial and ovarian lesions.⁴⁶ In some rural communities, because of a shortage of trained medical personnel, lay-women have been successfully trained to take smears.⁴⁴ Using nurses to take Pap smears should not be a threat to doctors, as it can be likened to other professions where proficient ancillary staff are employed to perform some of the more routine, but nevertheless, important tasks. This would spare the more highly-qualified professionals to deal with other intricate and complex problems.⁴⁴ The employment of pathology assistants is a good example of how pathologists can be helped by the use of well-trained but less qualified staff.⁴⁷

'Pap' smears need to be taken regularly

The age at which screening should commence should be just prior to when the first cases of invasive cancer occur, as the aim is to prevent invasive cancer from developing, as well as to detect precursor lesions. In Hong Kong, the first invasive cancers occur in women in their mid-twenties.^{1,48} One screening schedule that incorporates the likelihood of lesion detection and cost-effectiveness recommends that women who are sexually active should be offered Pap tests every 3 years from age 20 to 69 years.⁴⁹ The first smear should be followed by a second smear 12 months later, so that a false negative result is detected. At age 70 years, women with normal smear results may stop having further smears. Cancer experts have recommended three-yearly Pap smears because this interval is almost as effective as annual screening in reducing the cumulative incidence of invasive cancer (90.8% versus 93.5% reduction).⁵⁰ Annual screening would detect the additional 2.7% of lesions, but would cost substantially more. One Pap smear in a lifetime can still provide some degree of protection; a South American study concluded that a single smear taken at 45 years of age could lead to a 25% reduction of cervical cancers.⁵¹ In Hong Kong, there are no universally accepted guidelines for screening frequency, age of onset, and age for cessation of screening. Consequently, local experts, after consultation, should draw up an appropriate screening schedule that can be adopted by the medical profession.

Conclusion

The Pap smear will only have a greater impact in Hong Kong when good-quality smears are submitted to laboratories, when laboratories have high standards,

and more importantly when there is increased cervical smear coverage of the many Hong Kong women who have not been previously tested. As the new millennium approaches, tackling the scourge of cancer with a vigorous prevention and early-detection campaign should be a top health priority for Hong Kong. The old adage "prevention is better than cure" has never been truer, especially in Hong Kong, where one in every three deaths is due to cancer.¹ One test worthy of greater support is the Pap smear and as already stated, "No other test ever invented has been as successful as the Pap smear in preventing cancer."⁵²

Hong Kong's economic success was achieved by the hard work of both the men and women of the community. However, the role of women is often not fully appreciated in a society where men still have the dominant role. A way of recognising the role played by Hong Kong women would be the implementation of a comprehensive Special Administrative Region Pap smear screening programme.

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Photographs for Pictorial Medicine

We invite readers to submit clinical photographs for publication in the Pictorial Medicine section in future issues of the *Hong Kong Medical Journal*. These should be clear photographs (please send two sets, preferably in colour) from interesting, informative, or unusual cases, accompanied by one or two paragraphs of summary case detail. In addition, a brief background and relevant references should be included. Submissions must include signed consent to publication from the patient, and may be edited as appropriate. The Journal will apply appropriate eye masking when required.

Please forward Pictorial Medicine contributions, and address requests for patient consent forms to the Managing Editor, *Hong Kong Medical Journal*, 10th Floor, 99 Wong Chuk Hang Road, Aberdeen, Hong Kong, China; Fax: (852) 2505 5577/3149; Tel: (852) 2871 8822/8888.