Chapter 6
Summary of data

Cervical cancer and screening

Incidence and mortality worldwide

The majority of cervical cancer cases today occur in the developing world. However, before the introduction of screening, the rates of cervical cancer in most of Europe, North America and Japan were very similar to those now seen in developing countries.

The reported incidence and mortality rates for different populations have different degrees of reliability. Even when cases of and deaths from cervical cancer are reported, they may be reported or recorded as 'uterus not otherwise specified (NOS)' rather than as cancer in the uterine cervix specifically. The rates of death from and cases of cancer of the 'uterus NOS' must be borne in mind when considering incidence and mortality rates of cervical cancer. A further influence on incidence and mortality rates in a population is the hysterectomy rate, since this affects the denominator used in the calculations.

Cancer of the cervix uteri is the second most common cancer among women worldwide, with an estimated 471 000 new cases and 233 000 deaths in the year 2000. Almost 80% of the cases occur in developing countries, where, in many regions, it is the most common cancer among women, responsible for about 15% of all new cancers. The highest incidence rates are observed in Latin America and the Caribbean, sub-Saharan Africa, and south and south-east Asia. Cervical cancer is less common in economically developed countries, where in the year 2000, it was estimated to comprise about 4% of cancers in women, ranking sixth in importance.

The demographic determinants of risk include age, marital status, socioeconomic status and ethnic and religious groupings.

Survival has not been shown to vary between populations when the data are corrected for clinical stage at presentation, provided that adequate and equivalent treatments are available, and that co-morbidities (e.g., HIV status) are taken into account. After major improvements in survival of cervical cancer patients in the first half of the twentieth century, there has been little additional progress in recent years. Indeed, it is an apparent paradox that, often, when screening has become established in a population, no improvement in survival is seen. This is chiefly because there usually remains a proportion of late-stage tumours which are diagnosed in women who were inadequately screened or not screened at all. These become important when calculating survival rates if the majority of the population is well screened and may avoid developing cervical cancer altogether.

Pathology of cervical neoplasia

Intraepithelial squamous lesions

HPV infection of cervical squamous epithelium leads to two categories of intraepithelial squamous lesions: productive, self-limited HPV infections, and those with potential to progress to invasive squamous-cell carcinoma. Biopsies of productive HPV infections of the cervix have been classified variously as *koilocytotic atypia, koilocytosis, condyloma, mild dysplasia, cervical intraepithelial neoplasia grade 1 (CIN 1),* and *low-grade squamous intraepithelial lesion (LGSIL or LSIL).* Lesions more likely to represent cervical cancer precursors have been classified as *moderate dysplasia, severe dysplasia, CIN 2, CIN 3, including carcinoma in situ,* and *high-grade squamous intraepithelial lesion (HGSIL or HSIL).* Many pathologists report histopathological diagnoses using more than one classification scheme.

Intraepithelial glandular lesions

Adenocarcinoma *in situ* (AIS) is the only well characterized intraepithelial glandular lesion of the uterine cervix. These lesions are less common than their squamous counterparts and are associated with persistent infection by high-risk types of HPV. The utility of diagnostic terms for intraepithelial glandular lesions with lower degrees of atypia than AIS, including *endocervical dysplasia, cervical intraepithelial glandular neoplasia,* and *endocervical glandular atypia*, has not been established.

Invasive squamous and glandular lesions

The World Health Organization classification scheme for tumours of the uterine cervix recognizes three general categories of epithelial tumours: squamous-cell carcinoma, adenocarcinoma, and other epithelial tumours. Three major pathological variants of invasive squamous-cell carcinomas are recognized: keratinizing carcinoma, large-cell non-keratinizing carcinoma and small-cell carcinoma. Risk factors for invasive glandular lesions overlap with those for invasive squamous lesions.

Diagnosis and treatment

Pre-invasive cervical lesions

By diagnosing and treating pre-invasive (pre-cancerous) lesions, the rate of invasive cancer can be reduced. Women with the minor intraepithelial abnormality of CIN 1 may be managed conservatively with cytology augmented by HPV DNA testing or repeated cytology according to established protocols. Those with a cytological diagnosis of atypical squamous cells, an equivocal epithelial abnormality, have a small increase in risk of underlying high-grade disease which may be detected by using HPV DNA testing, or repeated cytology and referral to colposcopy. Women without CIN 2 or 3 may resume routine screening according to protocols.

Treatment of CIN 2 or 3 lesions may involve destructive or excisional techniques. Meta-analysis indicates little difference in success or morbidity in relation to the different techniques, which include cryotherapy, loop excision, and laser vaporization. The loop electro-surgical technique (LLETZ or LEEP) for transformation zone removal has become the standard way of treating CIN in developed countries; cryotherapy has been shown to be effective and safe in developing countries. The 'see-and-treat' method, where the excision is performed at the first diagnostic colposcopy visit, depends on expert assessment of the atypical transformation zone, usually by colposcopy in developed countries in the presence of a report showing high-grade cytological abnormality, but by the trained examiner in developing countries. Treatment failures (overall rates of 3–7%) are most likely to occur in women aged over 50 years with involved resection margins in the excised histological specimen.

Women with immunosuppressive states, for example due to HIV infection, are at increased risk of having high-grade CIN and need intensive follow-up after treatment in view of a higher recurrence rate.

After a check-up at six months with colposcopy and cytology, follow-up can be based on cytology alone at yearly intervals up to 10 years, with colposcopy in case of any cytological abnormality to judge the need to take biopsies or for re-treatment. Adding HPV testing gives more sensitivity and is quicker than follow-up cytology in detecting recurrent disease.

Cervical cancer

The rates of cure of cervical cancer depend on the stage at which diagnosis occurs. Diagnosis is by examination of a woman with suspicious symptoms or uncommonly as a result of abnormal cytology. The earliest pre-clinical stages of invasive disease (stage IA or micro-invasion) can be managed conservatively by excisional procedures with nodal sampling. At a more advanced stage (IA2), radical excision of the cervix and associated para-cervical tissue (radical trachelectomy) in women with fertility aspirations can be applied, but when fertility is not important, hysterectomy with associated lymph node sampling is recommended.

Staging of clinically invasive cancer involves a multi-disciplinary approach including radiological examination to assess the extent of invasion within the cervix and its surroundings. Early clinical invasive disease (stage IB1) may be considered for radical cervical removal as described for stage IA2. The usual procedure for a tumour of diameter above 4 cm (stage IB2) is radical hysterectomy combined with radiotherapy with or without simultaneous chemotherapy. Nodal sampling is mandatory.

For more advanced disease (IIA–B) with cervical and parametrial-vaginal extension, radiotherapy with concurrent chemotherapy with cisplatin derivatives is indicated; this regime has been associated with improved survival.

Stage IV cancer with recurrent or refractory disease with associated high mortality rates represents a challenge to radical pelvic surgery in limited cases but chemo-radiation is the usual treatment modality.

Palliative care is a basic need in any cervical cancer screening programme. No matter what the availability and accessibility of cancer treatment, palliative care services and medications should be provided according to standards recommended by WHO.

Etiology

Cervical cancer is an uncommon outcome of a common sexually transmitted infection. The causal association is restricted to certain genotypes of the human papillomavirus (HPV) family, denoted as high-risk types. Infections of the epithelium with HPV are usually of transient nature and may lead to the generation of an immune response, of which cellular immunity seems to be the most important for regression. Any event inhibiting normal differentiation of the epithelium or prevention of the normal sequence of viral replication may lead to the development of persistent infections, which can remain

clinically latent or become active due to a compromised immune status or other factors.

Infection of the cervix with HPV occurs during sexual intercourse with an HPV-infected male. Other forms of HPV transmission are of little relevance to genital tract infections.

The age at first exposure to HPV and the age-specific HPV DNA prevalence are strongly related to the patterns of sexual behaviour and are therefore population-specific. The risk of HPV infection and the risk of cervical cancer in a woman is directly related to the number of lifetime additional sexual partners of her sexual partner and to the number of sexual contacts with prostitutes. Male circumcision offers some protection from both HPV infection and cervical cancer in the spouse.

The development of a long-term persistent infection is required for progression towards cervical cancer. Factors possibly affecting persistence include HLA class I antigens, HLA class II haplotypes, polymorphisms in certain human genes (such as p53), partly in combination with viral variants, loss of heterozygosity and epigenetic events leading to the loss of cellular protein expression. Events compromising the immune system increase the frequency of persistent infections and consequently the risk for malignant progression.

The association of high-risk HPV types and cervical cancer is causal in nature and, under optimal testing conditions, HPV DNA can be identified in all specimens of invasive cervical cancer. The association is consistent worldwide and includes the squamous-cell carcinomas, the adenocarcinomas and the vast majority (>85%) of the high-grade precursors of cancer (CIN 2 and 3).

The recognition that HPV infections are a necessary cause of cervical cancer has several profound implications for cancer prevention. Firstly, in the absence of persistent viral infection, cervical cancer is not expected to develop. Consequently, preventive strategies based on HPV screening or prophylactic vaccination should be viewed as targeting virtually all cervical cancer cases. Secondly, the distribution of HPV types in cervical cancer cases shows a strong predominance of HPV 16 and 18. The 13 most common types account for an estimated 98% of the cancers worldwide. Thirdly, the risk estimate for any of these 13 types is not statistically different from the risk linked to the most common types, HPV 16 or 18. Therefore, the use of a probe set including high-risk HPV types in screening and patient management is justified.

Co-factors that further increase the risk of invasive cancer among HPV DNA-positive women include increasing age, the long-term use of oral contraceptives (five or more years), high parity (five or more full-term pregnancies), smoking and HIV. Co-factors that possibly increase cancer risk include previous exposure to *Chlamydia trachomatis* and herpes virus type 2.

The age at first exposure to HPV and the age-specific HPV DNA prevalence are strongly related to the patterns of sexual behaviour and are therefore population-specific. To make efficient and effective age-specific recommendations for HPV screening, the HPV attack rate and the age-specific incidence of invasive cancer should be described.

Principles of screening

When cancer precursors can be detected by screening tests, as for cancer of the cervix, the aim of screening is to reduce the incidence, and as a consequence also the mortality from the disease. Screening programmes are directed to populations, but dependent on individuals accepting the invitation to be screened and administration of a high-quality screening test. Subsequent diagnostic tests and treatment are required for those found to be test positive. Ethical issues are important. Women should be aware that screening cannot prevent all cases of invasive cancer occurring and should be informed of the processes and consequences of screening.

Natural history of cervical cancer

Studies of the natural history of cancer of the cervix based on cervical cytology have been of two types, one based upon the invasive cases of the disease and reconstruction of the natural history retrospectively, often using a case–control design, the other on cohort studies following up women who had been screened. Studies incorporating HPV testing have been predominantly cross-sectional or cohort in type. The earlier cytology-based studies had histologically confirmed carcinoma *in situ* or invasive cancer as the end-point; more recent studies have concentrated on various degrees of CIN, some based only on cytological diagnoses. Several studies have modelled the data from other reported studies.

Most precursor lesions arise within a specific region of the cervix that is referred to as the transformation zone. The transformation zone appears to be particularly susceptible to neoplasia induced by high-risk types of HPV.

Current theories of the pathogenesis of cervical cancer consider infection of the cervical epithelium with specific high-risk types of HPV to play an integral role in the pathogenesis of cervical cancer and its precursor lesions. There is good evidence to support a model of cervical cancer pathogenesis involving a multistep process. Infection with high-risk types of HPV is the first stage in this process. HPV infection of young women is frequent, and transient in the large majority of

women. The median duration of a prevalently-detected HPV infection is typically about a year for high-risk types of HPV and shorter for the low-risk types. The greatest determinant of clearance of HPV infection is age (maximal in young women) and HPV type (lowest in those infected with HPV type 16). Many women with transient HPV infections will develop cytological abnormalities. When HPV is actively replicating in cells, it can produce characteristic cytopathic effects and borderline or mild cytological abnormalities. Borderline or mild cytological abnormalities are most commonly identified within the first six months of initial infection. In some women with transient infections, colposcopy reveals CIN 1 lesions. A small proportion of women who become infected with HPV develop persistent HPV infections. The biological reasons why some women develop persistent infections are poorly understood.

The great majority of invasive cancers develop after a pre-invasive stage of sufficient length to allow their detection by screening programmes. Persistence of high-risk types of HPV is a prerequisite for the development of CIN 3 lesions and invasive cervical cancers. A variety of natural history follow-up studies based either on cytology alone or using a combination of colposcopy and cervical biopsy have demonstrated that CIN 1 lesions have a relatively high rate of spontaneous regression in the absence of treatment and low rates of progression to higher-grade CIN or invasive cervical cancer. In contrast, CIN 3 lesions and carcinoma *in situ* lesions have much lower rates of spontaneous regression and higher rates of progression to invasive lesions. The biological behaviour of CIN 2 lesions taken in aggregate appears to be intermediate between that of CIN 1 and CIN 3 lesions in terms or rates of progression, regression and persistence.

Cervical cancer precursors can be defined in a variety of ways including virological measures, biological features and morphological terms. Cellular properties of the majority of invasive cervical cancers and many precursor lesions include monoclonality and aneuploidy. Other cellular events include genetic alterations which may result in the activation of oncogenes and inactivation of tumour-suppressor genes, and increases in telomerase activity. There are a number of inherent problems in many prospective studies of the natural history of cervical cancer precursors. Therefore critical parameters including the rate of progression from precursor to invasion and the proportion of precursors that will progress if left untreated may be poorly characterized. However, it is clear that progression occurs only in HPV-positive women, with very low probabilities of progression in women under the age of 30 years. Estimated progression rates in studies of older women have varied depending on the end-point used. For CIN 3 or carcinoma i*n situ,* the progression rates approximate to 50%, though lower rates have been reported, and rates are higher in studies of prevalent disease, and in older than younger women. For CIN 2 or moderate dysplasia or less, all studies have estimated progression rates of 20% or less.

Regression is an important part of the natural history of both carcinoma *in situ* and dysplasia (CIN), though the estimated extent of regression has varied, from about 30% of cases of carcinoma *in situ* or CIN 3 at ages above 50 to 70% at younger ages, while for moderate or slight dysplasia (CIN 2 or less), the majority of lesions regress within five years.

Screening tests

Cervical cytology

Cytological testing involves collection of exfoliated cells from the cervix and microscopic examination of these cells after staining. This allows abnormal cells to be detected and an estimation of whether there is an underlying cervical cancer precursor, so as to determine whether the woman needs further follow-up.

Cytology-based screening programmes continue to be the mainstay of cervical cancer prevention worldwide. Over the last two decades there have been major changes in the terminology used for reporting results. In most areas of the world, either the World Health Organization terminology, the cervical intraepithelial neoplasia (CIN) terminology, or the 2001 Bethesda System are used to classify intraepithelial squamous lesions. It is important that cervical cytology specimens be assessed with respect to their adequacy and that a uniform terminology be utilized for borderline cytological changes that are not diagnostic of an intraepithelial lesion. In many countries these borderline specimens account for 3–5% of all specimens and for up to 50% of all women with biopsy-confirmed CIN 2 or CIN 3.

With newer liquid-based cytology (LBC) methods, epithelial cells scraped from the cervix are transferred to a liquid fixative and transported to the cytology laboratory for processing. The unit cost for LBC is considerably higher than that of conventional cytology. Purported advantages of LBC over conventional cervical cytology include a more representative transfer of cells from the collection device to the glass slide, a reduction in the number of unsatisfactory specimens, the possibility of using residual cellular

material for additional molecular testing, and a statistically significant increase in detection of HSIL. However, LBC systems differ in their test characteristics, and data obtained from earlier systems cannot necessarily be extrapolated to new systems.

The importance of training to ensure proper specimen collection cannot be overemphasized. One-half to two-thirds of false negative cervical cytology results are a result of either poor patient conditions (such as active menstruation or severe cervicovaginal infections) at the time the specimen was collected or the manner in which the specimen was collected. It is critical that the entire transformation zone be sampled during specimen collection, since this is the area where almost all CIN 2 and CIN 3 lesions develop.

Adequate quality control and quality assurance programmes are critical to maintaining a high level of performance in a cytology service. These need to provide continuous monitoring of record-keeping, review of abnormal cases by a cytopathologist, review of negative cases either by a 10% rescreening programme or by use of a rapid prescreening or rescreening of all samples, correlation of cytological and histological results from abnormal specimens whenever possible, and proficiency testing programmes. It is also important to set upper and lower workload limits.

Visual inspection

Sensitivity of visual inspection with application of acetic acid (VIA) or with Lugol's iodine (VILI) has been found similar to that of cytology for detecting CIN 2–3 or invasive cancer in some developing countries, but specificity is lower. In one large study, VILI showed better sensitivity and potentially better reproducibility. VIA with magnification has not shown any advantage over VIA using various low magnification devices. The low sensitivity of unaided visual inspection precludes its use as a screening test.

Visual inspection tests are inexpensive, safe and acceptable techniques, and require a lower level of infrastructure than laboratory-based tests. They can be performed by a wide range of personnel after a short period of training, and test results are available immediately.

There are no universally accepted definitions of test results for VIA and VILI. Visual inspection methods are subjective and present challenges to maintain the quality of testing. Adequate training and supervision are critical to implement visual inspection-based screening.

Colposcopy

Despite the extensive reliance on colposcopy, understanding of how to optimize its performance as a diagnostic or screening test is still incomplete. Recent studies show that colposcopy-directed biopsy has sensitivity for detecting CIN 2 or worse lesions as low as 57%. Colposcopists are well able to differentiate high-grade lesions from other conditions, but differentiation of low-grade changes from normal tissue is more problematic. Relatively few studies have been performed to assess the accuracy of the Reid scoring system, but it appears that there is scope for improvement.

HPV DNA testing

Research on the use of HPV DNA testing as a potential cervical cancer screening and management tool began in the late 1980s in response to the evidence that these viruses play a causal role in cervical carcinogenesis and that HPV testing of cervical cells could have acceptable diagnostic performance, while being more reproducible and more easily adapted for clinical practice than conventional cytology.

Techniques to detect the presence of HPV in cervical cell specimens have evolved considerably in the last 25 years and have included methods based on cytological, immunocytochemical and nucleic acid hybridization principles. The Hybrid Capture™ (HC) assay and polymerase chain reaction (PCR) techniques are among the most common and represent signal and target-amplified DNA hybridization approaches, respectively. The former has become an approved technique for screening and triage of equivocal cervical abnormalities in many developed countries. Acceptable standards of testing formats are constantly evolving but in essence, they are based on the principle of detecting, either individually or jointly, the main types of HPV that are associated with cervical cancer. Research is continuing on reproducibility and on agreement between test formats; such performance characteristics must be calibrated with respect to detecting cervical cancer precursors and not merely the presence of HPV in cervical specimens.

For primary screening of women older than 30 years of age, HPV testing yields on average about 10–20% greater sensitivity and 10% lower specificity than cytology (either conventional or liquid-based). In some studies, the combination of cytology and HPV testing (as independent or reflex testing) attained very high sensitivity and negative predictive values (approaching 100%). A testing combination with such a high negative predictive value could potentially allow screening intervals to be increased, e.g., from the minimum of three years up to five years or longer, depending on the population and risk profile. The drawback of this approach is the loss in specificity with respect to either test in isolation due to the excessive number of patients who would need to be referred for colposcopy.

The high unit cost of HPV testing and the fact that it is not a public domain technology, like cervical cytology, remain important impediments to its wider acceptance in cervical cancer prevention. The cost-effectiveness of HPV testing is heavily dependent on assumptions related to the cost of the test, the infrastructure available in the setting where the screening will be implemented, the length of the interval between screening visits, and the existing expenditures incurred by quality assurance imposed by local legislation. More studies are needed in low-, middle- and high-income countries to assess effectiveness as a function of these variables.

Although there are no additional physical hazards associated with HPV test in cervical cancer screening, reservations are nonetheless noted. Little is known about the psychological and emotional impact of communicating positive HPV test results to women. If it were eventually implemented in primary screening for cervical cancer, testing for HPV would result in a large proportion of women having to be told that they harbour a sexually transmitted viral infection that can ultimately cause cancer. There is a dearth of research on the merits and consequences of conveying this information. Understanding of the dynamics of sexual transmission of HPV infection is insufficient for health providers to convey meaningful information on risk to men and women.

Other emerging techniques

Computer-assisted reading of cervical smears

Automation-assisted screening is aimed at increasing the sensitivity of cytological testing by finding, for instance, small abnormal squamous and glandular cells which are very difficult to find in conventional screening; it should also increase specificity by selecting only lesions corresponding to objective and reproducible criteria. Automated screening is designed also to increase productivity by excluding normal slides or part of the slides from manual screening by selecting most the atypical images from a slide to be checked by the cytologist.

The few randomized prospective studies and other performance studies have shown that automation-assisted screening may be applicable as a part of routine primary screening and can perform at least as well as conventional screening.

A new generation of automated devices for liquid-based cytology is now being launched, the performance of which has not yet been evaluated in randomized trials.

Physical real-time devices allowing an instant machine-generated result without requiring highly trained personnel hold promise, but have been insufficiently evaluated.

Molecular surrogate markers

Certain DNA, RNA or protein markers associated with the neoplastic transformation process subsequent to HPV infection may be applicable in screening, diagnosis and prognosis. Potential advantages from the use of such markers in clinical practice include: triage of women with minor cytological abnormalities (atypical squamous cells of undetermined significance (ASCUS) and LSIL) with higher specificity than HPV DNA detection; selection of women with lesions with high potential of progression needing treatment; prognosis prediction; improvement of the accuracy of histology as the gold standard for screening test assessment, by more accurate and reproducible classification of histological squamous and glandular cervical lesions and clearer distinction between cervical and endometrial glandular lesions; and last but not least, more accurate primary screening for cervical progressive cancer precursors.

Correlation studies have documented the presence or absence of certain molecular markers in cytological or histological material from selected patients. Test accuracy measures can be assessed for detection of CIN 2, CIN 3 or cancer, but are not representative for real screening, triage or follow-up settings. No such markers have yet been validated for use.

Combination of different modalities

Adding a sensitive detection method for high-risk HPV DNA to cytology yields a substantial increase in test sensitivity and negative predictive value for CIN 3 or cancer and probably allows an increase in screening intervals. The concomitant decrease in specificity is of particular concern for large populations. Cost-effectiveness analyses are still hampered by lack of long-term outcome data and information on psycho-social effects of mass HPV screening. The additional gain in sensitivity from adding cytology to HPV testing often is minor or negligible. Adding an HPV test to visual inspection in resource-poor settings is impractical because of the cost.

A second test can be used sequentially as a triage method where the purpose of the second test is to restrict the number of screen-positive women requiring referral. Among women showing equivocal cytology results, HPV DNA testing is more accurate for detecting underlying CIN 3 or worse disease than repeat cytology. HPV DNA testing is not useful for triage of mild cytological lesions with very high HPV positivity (e.g., LSIL as interpreted in the USA).

Colposcopy finds its place in the follow-up of cytological screen-positive women to decide the need for biopsy and to orient biopsy or excision for diagnosis or treatment. Negative colposcopic findings are not conclusive of

absence of high-grade cervical disease because of the intrinsic false-negative rate and the difficulty of observing localized endocervical disease.

Use of cervical cancer screening

Delivery and uptake of screening

Europe

Europe has several well organized and documented cervical cancer screening programmes at national and regional levels, but opportunistic screening activity is still predominant in most countries. Most countries recommend three-year screening intervals from age 25 to 64 or 65 years, but a few countries recommend five-year intervals and some one-year intervals. This results in large differences in the lifetime number of recommended screening tests across countries.

The reported statistics on screening activity and performance, available for a few countries or regions, mostly for organized programmes, are not always comparable. Most screening activity is not documented and there is an almost complete lack of information for some countries, especially in eastern Europe. Attendance above 80% or in the 70–80% range is found in a few countries, especially in the presence of organized programmes and in northern Europe, while levels of 60% or below are found in other countries, especially in southern Europe. Excess testing is substantial in most countries, with the exception of England and a few other areas.

The organization of screening delivery, cytological classification and management of women with abnormal test results varies between countries. Guidelines or regulations related to quality assurance, mainly of cytology, exist in different countries. Systems to ensure compliance with follow-up recommendations are adopted in organized programmes.

USA and Canada

In the USA, screening is mainly opportunistic, with only about 1% of the population being covered by a national cervical cancer screening programme administered by the Centers for Disease Control and Prevention (CDC). In the opportunistic service, payment is largely the responsability of the individual woman. New cervical cancer screening guidelines mostly recommend annual cervical cancer screening from age 21 until age 30 for conventional testing or every two years for liquid-based testing, and every 2–3 years between age 30 and 65–70 if previous tests were normal. Figures from the National Health Interview Survey show that screening coverage in the past three years is 82% in women aged 25 and older. Quality of cytology testing is regulated at the national level. Recommendations for follow-up of abnormal cytological test results now also include HPV DNA testing.

In Canada, screening is mostly opportunistic, with the services being reimbursed by provincial health plans. Some provinces have organized cervical cancer screening programmes for women aged 18–69 years, to which, once enrolled, women are invited at regular intervals. Population-based recruitment plans have not yet been implemented. Canada has issued screening and follow-up recommendations. New recommendations from 2003 include use of liquid-based testing and HPV DNA testing. Survey data show the three-year coverage to be 79% for women aged 20–69 years.

Latin America and the Caribbean

Attempts to organize screening programmes have failed in most Latin American countries, in spite of a coverage of over 60% reported in many countries. Long-standing organized screening programmes are in operation in Colombia and Chile, and are beginning to show reduction in incidence and mortality. In the rest of the region, there has been a lack of attention to quality assurance of cytology and, in many instances, lack of follow-up, diagnosis and treatment for women screened positive.

Africa

Many studies have concluded that providing cervical cancer screening services in sub-Saharan Africa is essential as this region carries a high burden of disease. However, access to early diagnosis and treatment is limited by severe resource constraints, competing health and development needs and dysfunctional health-care systems. The challenge for Africa is to develop screening services integrated into existing health services in such a way as to improve the overall functioning of health-care systems.

Oceania and Asia

Australia and New Zealand have established organized national cervical cancer screening programmes, while China (Taiwan) and the Republic of Korea have recently initiated screening programmes. All programmes use cytology and screen women every 2–3 years, targeting women aged 30 years and over in China (Taiwan) and the Republic of Korea and aged 20 years and over in Australia and New Zealand. These screening programmes have management structures for administration and quality assurance, and collect data to monitor performance indicators. Visual inspection with acetic acid is under trial in India and Thailand for possible use in screening. Outside of the few organized screening programmes, most women do not yet have access to screening for cervical cancer.

In Japan, an organized nationwide cervical cancer screening programme was initiated in 1983. Although government financing was phased out in

1998, the organized screening programme is still offered by each regional government. Annual screening by cytological testing is recommended to begin at age 30. There is no recommended age to end screening. One-year coverage in Japan is estimated to be about 25%. In April 2004, the Ministry of Health, Labor, and Welfare issued new recommendations stating that screening should be initiated at 20 years of age with an interval of two years.

This screening programme also stipulates the establishment of Management Control Committees that organize screening delivery and quality assurance and monitor performance indicators.

Behavioural considerations in screening participation

Factors associated with participation in cervical cancer screening include: having a contact with the health system, a good patient–physician relationship, a female screening provider, and providing the screening test in a setting where privacy is assured. In many countries, an invitation letter increased attendance. However, this procedure may be difficult to implement in low-resource settings.

Multi-component interventions that include education, home visits and involving family and key community members appear to be effective in increasing uptake among hard-to-reach women.

Efficacy of screening

In evaluating the efficacy of screening, it is preferable to have data from randomized screening trials. However, no such data are available with the incidence of clinical invasive cancer of the cervix as the end-point. The data available come from observational studies of screening in defined populations: cohort and case–control studies, which may not be free of bias, and studies of incidence and mortality trends which could be affected by changes in the impact of risk factors for the disease. For new screening modalities, the data available are generally from studies that compared the sensitivity and specificity of different screening tests, allowing estimation of relative sensitivity of the tests in detecting cervical cancer precursors.

For conventional cervical cytology, studies using cohort, case–control or geographical correlation (before/after analysis) designs indicate substantial effects in reducing the cervical cancer incidence and mortality rates, the impact exceeding 80% among women screened in various organized settings. Studies in Scandinavia, the United Kingdom and British Columbia, Canada, have been most informative. There is evidence that the screening impact is particularly large in the organized screening programmes. Opportunistic screening has also been found to reduce cervical cancer incidence, although generally to a smaller extent than in organized programmes, and requires far more resources.

There is evidence that the duration of the low risk after a negative cytology screening test is less in women under the age of 35 years than in older women. However, the incidence of invasive cancer of the cervix is extremely low in women aged less than 25, while in women aged 25–34 there is a low absolute risk of invasive cancer of the cervix after a negative screening test during the following three years. In women over the age of 35, and especially over the age of 50, the risk of invasive cancer of the cervix after a negative test is low for the next five years.

The evidence does not support annual screening at any age, a repeat test one year after the first test, nor screening after the age of 65 in cytologically negative women.

Meta-analyses have shown that liquid-based cytology is at least equivalent to conventional cytology in terms of relative sensitivity and specificity. There are insufficient data to evaluate the efficacy of currently available automation-assisted cytological screening systems, although data using a system that is no longer commercially available suggest that automated systems can be as sensitive and specific as high-quality conventional cytology. There are no long-term studies of impact on incidence or mortality using either of these new technologies.

Over a dozen studies have shown that testing for high-risk HPV is substantially more sensitive (around 95%) for detecting CIN 3 than conventional cytology (around 70%). Two studies have found a lower rate of CIN 3 on follow-up of HPV-negative compared to cytology-negative women, suggesting that the screening interval can be safely lengthened following a negative HPV test. Studies looking at archival smears and antibodies in stored sera indicate that HPV is present several years before the diagnosis of cancer or CIN 2/3 in cytologically negative women. The data suggest that testing for HPV infection, the necessary cause of cervical cancer, possibly at a longer interval than for cytology, may lead to lower invasive cervical cancer rates, but there are no data on cancer incidence or mortality rates after HPV screening.

Unaided visual inspection (also referred to as downstaging) is associated with low sensitivity (30–50%) to detect cervical cancer precursors and is no longer considered to be a suitable screening test. Naked-eye visual inspection after application of 3–5% acetic acid (VIA) and VIA with low-level magnification (VIAM) have similar test characteristics and VIAM has been shown to have no advantage over VIA. VIA has been evaluated in several cross-sectional studies, mostly in developing countries. In most cross-

sectional studies comparing VIA with conventional cytology, similar or higher sensitivity but lower specificity was seen. VIA is also being investigated in three randomized controlled trials in India for which early results are available from two cluster randomized trials. Rates of detection of CIN 2/3 lesions by VIA were similar in both trials (7/1000). A significantly higher frequency of stage I cancers (35–48%) was observed in the VIA screening group compared to the control group (0–24%). However, the detection rate of CIN 3 by VIA was significantly lower than by cytology in one trial.

Pooled results from 10 cross-sectional studies of visual inspection with Lugol's iodine (VILI) screening in India and Africa indicate higher relative sensitivity and similar specificity to VIA.

No significant difference in the performance of cytology in HIV-positive and HIV-negative women has been found. There are increased incidence and prevalence of HPV infection, intraepithelial lesions and cervical cancer among HIV-positive women compared to uninfected women. However, the impact of these data on the efficacy of screening in HIV-positive women is not clear.

Effectiveness of screening in populations

Incidence and mortality trends in relation to screening

Time trends in the incidence and mortality rates of cervical cancer are of considerable interest, as they may shed light on changes in exposure to etiological factors and provide a means of evaluating the success, or otherwise, of screening programmes. Comparisons of trends in the Nordic countries have been particularly informative. Decreases in incidence and mortality since the late 1960s were greatest in Finland, Sweden and Iceland, which had the most extensive screening programmes, and least in Norway, which had organized screening in only a single county.

Cervical cancer incidence and mortality rates have generally declined in the last few decades in many other populations in Europe, the USA, Japan and Oceania. However, there have been periods of increase, particularly in women under 35 years of age, in some areas, although these have occurred at different times in different countries. Observation of these trends has sometimes (e.g., in the United Kingdom) resulted in changes in screening practices, in order to attempt to reverse the upward trend. Cervical cancer mortality rates have been rapidly rising in a number of eastern European countries where there is little screening; this trend may have been reversed recently in the more affluent parts of eastern Europe.

There is less information on time trends in cervical cancer in developing countries. Rates of incidence and mortality have generally been stable, or shown modest declines. This probably reflects the lack of screening programmes, or, where they exist, their low coverage and/or poor quality.

The overall trends in cervical cancer incidence largely reflect trends in squamous-cell carcinoma, the dominant morphological type, and the type for which screening techniques have historically been more effective. Increases in cervical adenocarcinoma have occurred in many countries, especially in young women.

Use of modelling in the design and evaluation of screening

Statistical models can be used to explore the relationships between screening test, policy and programme characteristics and the expected reduction in incidence and mortality (and derivatives such as years of life saved). Simulation models have been developed that use observed data on disease natural history, screening test performance and effectiveness of different treatment options for precancerous lesions and can allow for heterogeneity of risk, accessibility, compliance and feasibility.

The quality of the models has improved over time as the underlying parameters (natural history, test sensitivity, etc.) have become better understood. The models have also become more widely used, as the contribution of the sophisticated methodology has become better appreciated and the statistical techniques more widely disseminated. As with any model, they are subject to the accuracy of the assumptions.

Use of such models has led to an improved understanding of the relative importance of various screening parameters and the relative gains to be expected; this can help screening programmes to infer where changes might be most effective.

Issues in the implementation of screening

The cytology test has been shown to be effective when well applied. Where cytology screening has failed to work, blame can be laid on the design or delivery of the screening service.

Demonstration projects can and should be used to ensure that screening of proven efficacy is implemented in an optimal manner for a given population.

Hazards of screening

The hazards of screening include anxiety and fear among women related to the difficulty of understanding the meaning of both negative and positive screening results, as well as the difficulty of understanding the concept of precancer. Further, there are problems related to the test itself, with both false positive and false negative

results, which may lead to either overtreatment or unnecessary medical interventions, or to undertreatment of significant lesions. Other hazards include the complications of treatment (cervical stenosis and incompetence leading to infertility) and the use of more medical therapies (e.g., hysterectomy) due to complications of treatment. Finally, in HIV-endemic settings and where HIV-positive women are not treated for HIV, cervical cancer screening may result in an inappropriate diversion of resources.

Performance evaluation

Cervical cancer screening should be implemented within the context of an established programme policy regarding age range and between-screen interval. A programme's policies will determine its maximal effectiveness. However, programme implementation and delivery will determine the actual effectiveness.

The essential elements for optimal effectiveness include identification of women in the target population; measures to guarantee high coverage and attendance; high-quality smear taking, reading and reporting; and methods to ensure follow-up of women identified by screening as having lesions needing further assessment. Indicators have been established to assess performance on these elements. The most important of these, in terms of effectiveness, is coverage or participation (proportion of women being screened). However, high coverage alone is not sufficient. If indicators in other areas, such as quality, are suboptimal, effectiveness will be compromised.

Performance indicators should be monitored regularly, preferably through routine systems of information. Where these do not exist, special studies such as population surveys and programme audits should be conducted periodically.

Cost-effectiveness

Cost-effectiveness models require data on natural history of cervical cancer, the overall effectiveness of the policy or intervention, survival rates associated with cancer, test characteristics, and quality of life. Sources could include: trials, observational studies, meta-analyses; other published literature, expert opinion and health systems statistics. Cost data must be collected locally or estimated according to local conditions. The eventual judgement as to whether a particular strategy is cost-effective or not will be dependent on local circumstances.

Common points are that expending resources on improving coverage and on achieving and maintaining adequate quality is almost always more cost-effective than any other potential service improvement and that opportunistic screening is less cost-effective than organized screening.