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Figure 1 (a) Mortality from cancer of the cervix uteri in nine European countries, 1998; (b) Trends in mortality from cancer of the uterus, Spain
From http:www-depdb.iarc.fr/who/menu.htm

peak or plateau in risk is unique for an epithelial cancer, and reflects the natury of infections with human papillomaus (HPV) and the related carcinogenic mechanisms. The age profile is readily distorted b screening and also, when cross-sectional data (from a single time period) are examined, by birth-cohort-specific changes in risk (Ashle, 1e66; Hakama & Penttinen, 1e81). In an attempt to define the age-specific incidence patterns of cervical cancer in the absence of screening activity, Gustafsson *et al.* (1997b) compiled incidence data for 28 different populations for long periods of time betw After scaling (to permit direct comparison betwies with incidence r of differing orders of magnitude), the rates for most populations fitted one of twerence curves used for descriptive purposes (Figure 5). The first group (*green line*), comprising Denmark, the former German Democr Repub, the Feder Germany (before reunification), the Netherlands, Norway, Slovenia and Sw 25, a rise betw a peak at ages 44–49 y. After the peak, the decline was fairly r

vices (especially screening) may be responsible for the observed differ-

High rates of cervical cancer have been reported among prostitutes (Rojel,

smooth estimates of survival as a function of time since diagnosis can be obtained. The actuarial method requires a life-table with survival times grouped usually into intervals that permit calculation of the cumulative probability of survival at time t

often do not allow distinction of precursor lesions that have a substantial capacity to progress from those lesions that do not, contributing to uncertainty for both clinicians and epidemiologists. Nevertheless, until more precise methods are developed for use in day-to-day settings, histological appearance remains the basis for the definition of both precancerous and cancerous cervical lesions.

Intraepithelial squamous lesions

Terminology

The uterine cervix is the cylindrically shaped lower third of the uterus that extends into the vagina. The cervix has a central opening or external os that opens into the endocervical canal which communicates with the uterine cavity (Figure 9). The cervical epithelium is derived from two embryologically distinct sources. The part of the

Cervical cancer and intraepithelial lesions that develop in the transformation zone can be visualized by colposcopy and diagnosed by histological examination of colposcopy-directed biopsies of areas that appear abnormal.

It is now generally accepted that squamous and glandular neoplasms of the cervix are caused by infection of cervical epitheliumized -0.1 (specific HPV)] TJ advances in the scientific and clinical understanding of cervical neoplasia.

At least three separate, but for the most part interchangeable, histopatho-

been classified as *moderate dysplasia, severe dysplasia*, *CIN 2, CIN 3*, *carcinoma in situ,* and *high-grade squamous intraepithelial lesion (HSIL)*. CIN 2 and CIN 3 lesions are usually associated with high-risk types of HPV, are monoclonal and are usually aneuploid (Fu *et al.*, 1983; Lungu *et al*., 1992; Park *et al et,al.*

(Ismail *et al.*, 1989; Price *et al.*, 2003). Many pathologists report histopathological diagnoses using more than one classification scheme. In this *Handbook*, the CIN terminology is used when referring to specific histopathological entities except when directly reporting studies that used different terminology.

"other" epithelial tumours (Table 3). The staging system developed by the International Federation of Gynecology and Obstetrics (FIGO Committee on Gynecologic Oncology and IGCS Guidelines Committee, 2000) is widely

al., 1983) and this diagnosis should be established only after clinicoradiological evaluation of extrauterine sites, together with immunohistochemical analysis to exclude a diagnosis of melanoma.

The clinical behaviour of invasive squamous-cell carcinomas may be predicted by a variety of histopathological features and ancillary studies. Tumour size, depth of invasion, parametrial involvement and nodal status are significant prognostic factors (Zaino *et al*., 1992; Kristensen *et al.,* 1999). The presence of HPV type 18 in invasive squamous lesions may be associated with worse clinical outcome (Burger *et al.*, 1995; Rose *et al.,* 1995; Nakagawa *et al.*, 1996). However, neither tumour ploidy status (Atkin *et al.,* 1990) nor cellular oncogene expression (Riou, 1988) has been established as an independent prognostic marker in invasive squamous lesions. *sq a.. a. ifAtO_*

carcinoma (Valente & Susin, 1987), villoglandular adenocarcinoma (Hopson *et al*., 1990), glassy-cell carcinoma

transformation-zone morphology that should be considered before undertaking excisional treatment—these are the size of the transformation zone, the position of the upper limit of the transformation zone and the visibility of this upper limit. These characteristics then identify the transformation zone ingmpleteltify,

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over four to five weeks in daily portions) and intra-cavitary therapy (brachytherapy, with the intention of achieving a total dose of 80–85 Gy to point A and 50–55 Gy to point B), so

influences progression. Most patients with stage I disease prefer caesarean section at the time of planned radical surgery, with vaginal delivery reserved for those with preinvasive or stage IA1 disease. Radical surgery and radiation offer similar cure rates, with the former being used for stages IA2, IB and IIA. Such pregnancies have, surprisingly, been associated with low morbidity and high survival rates when surgery is used (Goff *et al.*, 2000). Retention of ovaries in young women is indicated. However, women with stage IIB or more advanced disease or those not medically fit are candidates for definitive radiation therapy, which should be initiated immediately after delivery. The actual application of radiation requires adaptation to the anatomical distortions created by the pregnancy and patients opting for primary radiation therapy who intend to have a primary termination should have this before external therapy begins

Follow-up

Once it was recognized HPV represents a necessary cause of cervical cancer, of the role of co-factors in case–control studies was required by analysis restricted to HPV-positive women. Among persis-

2002; Clifford *et al*., 2003i; Muñoz *et al.*

For the relationship between cervi-

The ORs for squamous-cell carcinomas were statistically significant and very high. Restricting the analyses to studies that used the GP5+/6+ HPV detection system, the adjusted OR for HPV DNA detection (the factor by which the reference risk of cervical cancer is multiplied if HPV DNA is detected) was 158.2 for any single type (95% CI 113.2–220.6). The risk of adeno- or adenosquamous-cell carcinoma in J0t countries (Algeria, Brazil, India, Morocco, Paraguay, Peru, The Philippines, Thailand) was estimated to be 77.2 (95% CI 41.2–144.8) (F.X. Bosch, personal communication).

The pool of IARC studies was large enough to provide type-specific risk estimates for 18 HPV types. Type-specific risk estimates and confidence

been associated with a fraction of cancers of the oral cavity and oropharynx and with conjunctival squamous-cell carcinoma.

5. There is low concordance of HPV types and HPV16 genomic variants between heterosexual partners.

HPV and sexual behaviour

Epidemiological studies of risk factors for HPV infection have clearly and consistently shown that the key determinants among both women and men are related to their sexual behaviour. The best studied risk factors are their lifetime number of sexual partners, the age at which sexual intercourse was initiated and the likelihood that at least one of the sexual partners was an HPV

course, reporting of extramarital affairs and history of STDs.

The importance of the male role was also suggested by early studies of cancer clusters within couples. One study reported that subsequent wives of husbands whose previous wife developed cervical cancer had an increased risk of cervical neoplasia (Kessler, 1977), and other studies showed that wives of men with cancer of the penis had a high incidence and mortality due to cervical cancer (Martinez, 1969; Graham et al., 1979; Smith et al., 1980).

Data from the Swedish Family Cancer Database showed that husbands of women with in situ or invasive cervical cancer had an excess risk of

when considered as groups. The associations with number of sexual partners are stronger for the oncogenic types than for non-oncogenic types (Franco *et al.*, 1995; Kjaer *et al.*, 1997; Rousseau *et al.*, 2000).

Most studies of concordance of genital HPVs in heterosexual couples, but not all (Baken *et al.,* 1995), havst found a relativsly poor correlation of

sequence identity, determined over the E6, E7 and L1 open reading frames (ORFs), with the reference sequence (Van Ranst *et al.*, 1992; Myers *et al.,* 1996).

Because of the low prevalence of some genotypes, as detected by different genotyping methods, it has been difficult to categorize these according to risk, so that only 11 genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56 and 58) have been consistently classified as high risk (Lörincz *et al.,* 1992; Bosch *et al.*, 1995; Walboomers *et al.*, 1999). In a recent analysis using

function of E6 proteins has been demonstrated, but physical interactions with several cellular factors resulting in the deregulation of the cell cycle or interference with DNA repair have been described (Mantovani & Banks, 2001). The key activity of high-risk E6 proteins is their ability to inhibit the function of p53 (Scheffner *et al*., 1990; Werness *et al.*, 1990). p53 is a sequence-specific

these cellular responses, high-risk papillomaviruses encode the E6 protein, which causes degradation of p53.

Replication cycle in the infected epithelium

The initial infection by HPV probably occurs in stem cells of the basal layer of stratified cervical epithelium associated hair follicles of the skin (Stanley, 1994; Schmitt *et al.,* 1996). HPV genomes are

Cellular gene polymorphism

Another seemingly important marker of risk is a single nucleotide polymorphism in codon 72 of the p53 gene. There are two structurally different forms of wild-type p53, containing either a proline (Pro) or an arginine

smoking cessation among women with minor-grade lesions further supports the role of tobacco smoking in HPV carcinogenesis (Szarewski *et al.,* 1996).

The IARC multicentric case–control study investigated the presence of antibodies against the common sexually transmitted agents to assess their effect on cervical cancer risk in the presence of HPV DNA. The results show that among HPV-positive cases and controls there is a residual 1.5- to-2-fold increased risk linked to herpes simplex virus type 2 (HSV2) and *C. trachomatis* exposure, suggesting an interaction with the oncogenic capacity of HPV.

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related to exposure to HIV, with a summary OR of 0.8 (95% CI 0.5–1.4) (Newton *et al.,*

Knowledge on the natural history of the disease will facilitate decisions on

a prevalently detected HPV infection is typically about eight months for high-risk types of HPV and 4.8 months for the low-risk types (see earlier in this chapter). If detected during follow-up following a negative cytological test, the median durations are doubled (Richardson *et al.,* 2003).

for HPV DNA using PCR. The data were analysed as a nested case–control study. Compared with women who were HPV DNA-negative on enrolment,

final diagnosis of HSIL in 51 (0.7% of the total studied) within 4–36 months. The women who developed HSIL had a higher viral load than those with transient infections. All these women developed cytological abnormalities before or at the time of the colposcopy that led to the diagnosis. In contrast, of 2432 women who were negative for HPV and followed for a similar period as for the HPV-positive women, only two developed HSIL. Nobbenhuis *et al.* (1999) concentrated on CIN 3 as the end-point, using cytology and HPV testing by PCR to monitor for an average of 33 months 353 women who had been referred to gynaecologists with mild to moderate or severe dysplasia.

175 767 women screened in Alberta, Canada. They concluded that the generation of new cases of carcinoma *in situ* begins in the 20–24 age group at a very significant rate and that carcinoma *in situ*

In the Ostör (1993) review of the natural history of CIN described above for low-grade lesions, none of the stud-

of high degree in the five-year interval after a negative cytological test was 0.010. For carcinoma *in situ* the probability was 0.012, while for microinvasive carcinoma it was 0.002. This compares with a probability of 0.010 for the development of frankly invasive carcinoma before the screening programme and 0.002 after the first [negative] test. Combining the probability of being diagnosed with *in situ* cancer with that for dysplasia of high degree, the authors estimated that 28–39% of such surgically treated preinasive cases would otherwise have progressed to invasive cervical cancer, and that 21% of the frankly invasive cases are preceded b a preinasive stage of shorter duration than the five-year interval betw stage.

Gustafsson & Adami (1989) used Swedish population-based incidence to model the natural history of carcinoma of the cervix (including carcinoma *in situ*). They noted that the maximum incidence of carcinoma *in situ* occurred at 30 years.The proportion of cases of incident carcinoma *in situ* that progressed to invasive cancer was estimated to be 12.2%, with a mean duration of carcinoma *in situ* of 13.3 years, and the preclinical phase of invasive cancer without screening lasted on averor four years.The also estimated that 15–23% of prevalent carcinoma *in situ* progressed to invasive cancer. The regression r *in situ,*

Dup Tdpmdue5.2Tw /TE1 vTe9c0 v9 91) 1 2w d t

of telomerase, with increased levels of telomerase are likely to be important.

An ideal test would indicate that an oncogenic HPV has already enhanced genetic instability and rendered infected cells susceptible to transformation, thereby facilitating the development of cancer. In this respect, it should have the ability to detect those progressive cytological abnormalities that are caused by high-risk HPV infections and to discriminate them from transient low-grade lesions and those that only mimic morphological criteria of the onset of dysplasia or harbour HPV as an independent, but simultaneous event. Such a test should have greater true biological sensitivity and specificity than cytology and could possibly solve two problems inherent to conventional cytology. It could clarify how to consider the ASCUS and LSIx cytological abnormalities which, as already pointed out, represent mostly transient infections or in the case of ASCUS mainly diagnostic uncertainty. The other problem that contributes to low sensitivity of conventional cytology is overlooking and/or misinterpreting abnormal cells, a problem that also ideally should be overcome by] TJ0 that fulfils the criteria specified above and avoids sampling errors.

Figure 27 attempts to encapsulate

difficult to use since it includes a number of different entities. These are

and

. Studies have
s of intra-observer and
variation with cervical

ment of the specimen adequacy, a general categorization and a descriptive diagnosis (Table 16). These categories assist clinicians by providing answers to three basic questions: (1) Do I need to repeat the cervical cytology? (2) Was the cervical cytology normal? (3) If the specimen was not completely normal, what specifically

positive and false negative cervical

positivity among women with ASC-H is almost as high as that of women with a high-grade squamous intraepithelial lesion (HSIL) cytological result. Therefore the recommended management of women with ASCUS and ASC-H differs (Wright *et al.,* 2002a).

Low-grade squamous

quite hyperchromatic. Unlike non-kera-

reasonable sensitivity (Martin-Hirsch ., 1999) and many spatula-type devices have extended tips designed to collect cells from this area. Either a moistened cotton swab or a brush-type endocervical sampler device (e.g., cytobrush) can be used to collect a second sample directly from the endocervical canal after the portio has been sampled (Koonings ., 1992; Kohlberger .,

spread the cells onto the glass

A number of different LBC techniques are in use worldwide. These include ThinPrep®, SurePath™, Cytoscreen™, Cyteasy®, Labonord Easy Prep, Cytoslide, SpinThin and PapSpin. The first two of these are approved for use in the USA by the Food and Drug Administration (FDA) and are the most widely used methods wrldwide. They are therefore the best characterized in terms of performance
With the ThinPrep method, clumps of cells and mucus are broken up by mechanical agitation and then the liquid preservative solution is filtered through a membrane filter with a pore sizap
epithelial cells while allowing contaminating red blood cells and inflammatory cells to pass through. The epithelial cells collected on the membrane filter are then transferred onto a glass slide and stained. This produces a relatively thin, monolayer-type preparation. The ThinPrep-2000 processor allo
at a time, whereas the newr ThinPrep-3000 processor is more fully automated and allo
ples to be processed at a time. In contrast, with the SurePath method, clumps of cells and mucus are broken

consensus expert panel diagnosis in cases of missing follow-up, and histological follow-up of HSIL combined with a balanced follow-up diagnosis of all other available follow-up data. The most common reference standard used in studies of LBC performance has been the expert panel review of selected cytology specimens. Unfortunately, with expert panel review, the

ies. The wide variety of study popula-
tions

in an LBC specimen, necessitating

on' fashion perform less well than those who receive formal training, the variability in training inherent in this approach is a cause for concern. Whenever possible, cytotechnicians should receive formal, structured, competence-based training in interpreting cervical cytology specimens. The International Federation of Cytology has an international qualification for cytotechnicians, which can be used to ensure that competence has been obtained.

control measure. The same group previously demonstrated that rapid prescreening was superior to 10% random rescreening in identifying cases that were missed (Arbyn & Schenck, 2000).

Cytology–histology correlations and clinical follow-up

If a laboratory has access to histological specimens obtained at the time of colposcopy for an abnormal cytological finding, it should compare all premalignant and malignant cytological results with the histopathological observa-

absence of specific characteristics, usually with low and high thresholds of positivity (Table 23). Only one of the six published studies reporting test characteristics of VI (Table 24) did not suffer from obvious verification bias (see Glossary and Chapter 4) (Basu [illegible] 2002); it found sensitivity to be low (< 50%) irrespective of the threshold used to define test

contains little or no glycogen and does not stain with Lugol's iodine, taking a bright mustard or saffron yellow colour. Atrophic

VILI appears to be greater than that of VIA.

Quality control

histological sample from the endocervical canal if the new squamocolumnar junction (and thus the entire

of findings and the test cut-off for what are the minimal criteria for abnormality.

Studies of diagnostic colposcopy

Two meta-analyses have been performed on the

agreement by quadrant (A, 78.3%; B, 81.3%; C, 85.3%; D, 82.7%) were not significantly different (≥ 0.3), despite the use of different colposcopes.

Similar agreement was obtained when

Cervigrams are interpreted using the categories presented in

cytology or HPV for screening, and to a possible role for cervicography in the triage of women with equivocal cytology. These topics are considered below in the section on combined techniques.

58, 59 and 68. A probe set for a few non-oncogenic HPV types (6, 11, 42, 43, 44) has been available for both the HC1 and HC2 assays but its utility has not been sufficiently investigated in clinical or epidemiological studies. It is often designated as probe A, whereas probes for high-risk HPV types are referred to as probe B.

HC2 is an entire system that can be used with a dedicated cervical sampler kit containing a special cervical conical brush and a vial with specimen transport medium (STM). The brush is designed for optimal collection of cells

sensitivity and permits the detection of less than 10 copies of HPV DNA in a mixture. Therefore, PCR has a lower threshold of molecular detection for HPV DNA than the HC assay. PCR is based on target amplification with type-specific or consensus or general primers.

sequences from several different HPV types because they target conserved DNA regions in the HPV genome. The amplified DNA products can be

PGMY09/11). This amplicon is immobi-

Study, country

samples for testing. Studies varied in terms of timing of collection, collection method, or whether or not visual methods for cervical inspection were used as adjunct screening techniquesor .

One advantage of HPV DNA test-

routine primary screening and with the devices tested it seems to perform at least as well as conventional screening in an organized well functioning programme. Automation-assisted screening may improve the results of a sub-optimal screening organization, but may have no advantage over a well organized, high-quality screening programme other than possibly handling more samples with same quality.

A new generation of automated devices for use with liquid-based cytol-

p16

Cyclin-dependent kinases (CDKs), cyclins and CDK inhibitors are ke k

Table 40. Overview of p16 immunoreactivity in histological material of lesion and HPV status

	Detection and and	p16 positivity	Lesion, HPV status	*N*	% p16+
Sano	-Mouse monoclolnal antibody (JC8)	Diffuse	-Mouse		

Mitchell, 2002). They become progressively shorter as cells multiply, resulting in chromosomal instability and senescence when a critical short length is reached (Counter ,
1992). The enzyme telomerase is a ribo-nucleoprotein composed of an RNA part (hRT) and a catalytic part (hTERT), which controls telomere length and is believed to play a role in immortalization of cells (Mathon & Lloyd, 2001; Blasco, 2002). Its activity is increased in CIN and cancer. The intensity of telomerase activity is reported to be correlated with the severity of the abnormality in biopsies and in cervical scrapings, but reliable detection of hTR, hTERT and telomerase activity is still limited by analytical deficiencies (Oh , 2001; Jarbte isCO_o

Sequential tests (triage)

The classical scheme of secondary cancer prevention consists of three steps: sensitive screening of asymptomatic individuals to identify those at risk of disease, specific diagnosis of the disease state and treatment of

treatment67 TwT T*/CREO_o9 BMC(cance3) TjEMC/CR1 BMC(diseas4) TjEMC_o31 BMC(diseas4) TjEMCT*/CREO_o9 BMC(canc

cytomorphological threshold utilized. Importantly, virtually all of the occult CIN 2 or 3 associated with ASCUS is found in the HPV-positive fraction. Therefore, in the context of ASCUS cytology, triage by HPV testing can

its characteristics as a screening test (Solomon, 2003). If used as a

ing the optimal management of women
diagnosed with less than

country affects the potential effectiveness of a cervical screening programme, in particular if only part of the service is free of charge or covered by insurance (state or other). Further

Country	Age group

GPs frequently act as advisers both in the presence and in the absence of personal invitations. Attendance following invitation was higher with letters signed by the GP than with letters signed by programme staff (Segnan *et al.,* 1998; Palm *et al.,* 1993). In the United Kingdom, GPs are paid for screening based on the coverage among their patients. This was introduced to increase coverage (Rudiman *et al.,* 1995).

The facilities for testing and the professionals involved vary widely between countries and between organized and opportunistic activity (Table

Country-takcerunicantion ofytolog(y)] TJEMC/CREO_213 BMC(resultks) TjEMC-0.0031 ck0 w22. TLn0.0.08-22. TTdntr usntriayGynaec

Where results are registered, the level of comprehensiveness varies. Comprehensive computerized registration of all tests is performed in the

effective organization not only reduces the cost of screening programmes but improves their effectiveness,

hysterectomy for a benign condition with adequate pathological documentation that the cervical epithelium has been totally removed and previous screening tests have been normal.

Two

for enforcing the regulations, and CDC provides technical and scientific sup-

- Patients must be properly examined and cervical cells from

cessive confirmed negative progr

Country

66.9%, respectively), largely due to family-planning programmes in their primary health-care infrastructure.

In other Latin American countries not covered by Health and Fertility Surveys, various studies have assessed screening participation in the population. The proportions of women

Dias-da-Costa *et al.,* 2003) and who report satisfaction with previous care (Alvarez, 1996; Brenna *et al.,* 2001).

Quality of cytology

Several cytology laboratories in Latin America and the Caribbean perform quality assurance procedures, by studying reproducibility, performance evaluation or cyto-histological correlation. In Mexico, two studies on reproducibility of cytological testing, as measured by weighted kappa, concluded that intra-class agreement was low for dysplasia and carcinoma

screening programme, national organized programmes that achieve high participation are required. Research in African settings confirms that integration of screening services into the existing health-care systems is the only way that high participation rates could be achieved (JHPIEGO, 1997).

These two provinces have the greatest access to screening services. In three provinces budgetary allocation for cervical screening exists. While in provinces such as Limpopo and Mpumalanga, poor transport systems are considered a barrier to implementation, as this hampers the delivery of slides to laboratories. However, other possibly poorer provinces have found creative ways of overcoming this problem, for example by linking cervical screening with the tuberculosis programme and using the same laboratory transport system. This illustrates the value of integrating cervical screening into existing health-care services. In another case, private taxis transport the slides as part of their routine runs. While in all provinces there are colposcopes at the district level, there may be no trained staff available to use them. In one rural province a partnership with a non-governmental organization has been set up to improve access to screening services and three of the five districts comprising the province report offering services. Nonetheless, in some instances women in the wrong age group are being screened. However, it is becoming increasingly clear what kinds of intervention are required in order to assist provinces to implement a programme. Pilot programmeas tve been set up and manuals for managers have been developed.

The South African experience has shown the need to provide health service managers with tools to assist

shorter intervals than recommended, with generally low-quality cytology. In addition, most women attending screening are of high socioeconomic status and probably are not the women at highest risk. About 150 000 tests are performed every year.

India

India has a National Cancer Control Programme that supports the principle of early diagnosis and treatment of cancer of the cervix. Although cytological testing is available to a limited population of mainly urban women, there are no screening programmes (Dinshaw & Shastri, 2001; Shanta, 2001; Varghese *et al.,* 1999). India is a high-risk country for cervical cancer (Shanta *et al.,* 2000; Sen *et al.,*

several health areas and outlines responsibilities for delivery of the national screening programme.

Extent of use and access
The screening programme

regional services are responsible for local management and data entry of laboratory results to the screening register. In addition, the NSU also funds some low-cost or free cytological and colposcopic services and treatment provided by District Health Boards.

An inquiry into the apparent under-reporting of abnormal results in the Gisborne region found that during the 1990s the NCSP lacked the necessary organization, coordination and some of the constituent parts required for safe and effective screening programmes. A ke

the reporting period, non-participation, re-participation, incidence of cervical cancer and incidence by stage, cervical cancer mortality, rates of cervical abnormality and histology abnormality reporting on the register, interval cancers, programme sensitivity, the opt-off r

survey respondents were aware that cytological testing detects abnormalities in asymptomatic women (Eaker

of respondents
of screening,
knew the type of
e screening test

Having had a test in the last three years associated with:ree

Test in the previous 12 months associated

countries (Nascimento *et al.,* 1996;

a. 55%
b. 67%
NS differences.

a. 28%
b. 13%
p<0.001

a. 36.9%
b. 22.6%
c. 25.9%
d. 24.5%
Letter

many women still report that their doctor failed to recommend screening. Seven of the studies included in Table 57 evaluated the effect of seeral types of physician reminder (including a flag reminder affixed to the woman's medical record) versus a control group with no intervention (Binstock *et al.* 1997; Burack *et al.,* 1998; McDow *et al.,* 1989; Ornstein *et al.,* 1991; Pritchard *et al.,* 1995; Pierce *et al.,* 1989; Somkin *et al.,* 1997). Only two of these studies found a significant increase in screening uptake compared with no intervention (Binstock *et al.,* 1997; Pierce *et al.,* 1989). Hower, no differences were found between the physician reminders and other types of intervo studies (i.evitations sent to women).

In the United Kingdom, target payments for GPs have been linked to the level of coverage achieved, with the payment for coverage of 80% or over being almost four times that for 50% to

ment for screen-positive women has been shown to be a feasible option in low-resource settings (Gaffikin *et al.,* 2003). One advantage of the "see-and-treat" or "screen-and-treat" approaches

programme is also dependent on the diagnostic methods that are used to augment colposcopy and biopsy (e.g.,

histological diagnosis available on those positive on one of the screening

lesions and cytology. This is because there will be more women selected for triage, which will increase the probability of detecting incipient lesions that would never be found were it not for the contribution of the

were to be used as the end-point, it must be recognized that those recruited into a screening programme are initially free of the disease of inier-est, so that it is not appropriate to apply population mortality rates for the disease to the person-years experience of the study cohort. Rather, as isrequired in estimating the sample size required for a controlled trial of screen-ing, it is necessary first to determine the expected incidence of the cases of

Table 59. Characteristics and main findings from the cohort follow-up studies on screening impact on cervical cancer

Location (reference)	
British Columbia,	

[a] Vital status or losses from follow-up were not reported.
NR, not reported
If not available in

for all attenders combined was 0.7. Among non-attenders, the estimated SIR was 1.6. The approximate relative risk (RSIR) between attenders and non-attenders was 0.7/1.6 = 0.44; and between test negatives and non-attenders 0.3/1.6 = 0.19 (confidence intervals not available). The long-term protection provided by screening sched-

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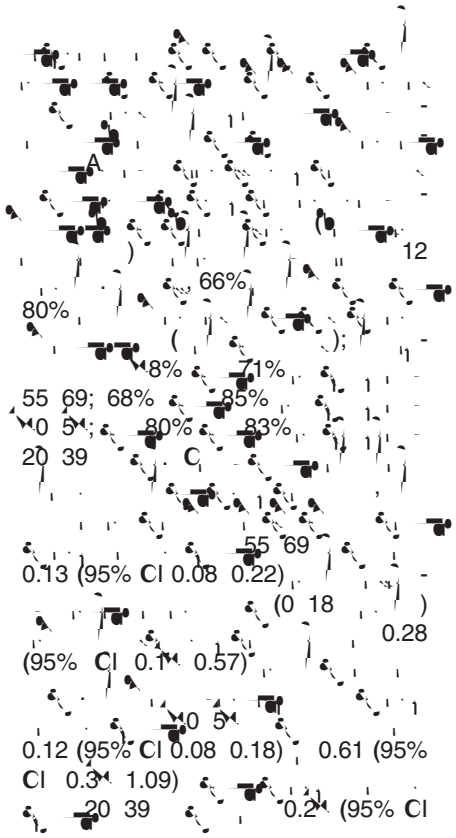
Ciatto (2000): three of these had been carried out in North America, two in Central America, four in Asia and five in Europe. Since then, another four case–control studies have reported effects of cytological screening by screening status (screened versus non-screened), in Mexico (Jiménez-Pérez & Thomas, 1999), Finland (Nieminen *et al.,* 1999), Sweden (Andersson-Ellström *et al.,* 2000) and South Africa (Hoffman *et al.,* 2003). Table 60 summarizes the main characteristics and findings of these studies.

About half of the studies were carried out within organized programmes or with active invitation of women.



Zhang *et al.,* 1982).

The IARC Working Group on Cervical Cancer Screening Programmes (IARC, 1986S established a proper approach to re-screening. This study

been modelled by the IARC (1986) study, and subsequently adopted as a suggested policy for South Africa (Provincial Administration Western Cape: Department of Health, 1995).

Miller *et al.* (2003) conducted a case–control study of cases of invasive cancer diagnosed between 1983 and 1995 within the Kaiser Permanente medical care programme (see above). The ORs for various intervals between screens, with a one-year interval as the referent, adjusted for ever having had an abnormal cytological finding before the last negative result and for having at least one negative result within 36 months before the last negative one,

England and Scotland. Women with prior dyskaryosis or borderline nuclear abnormalities had RRs for a positive test after the age of 50 of 4.39 and 3.08, respectively, compared with women whose screening history before the age of 50 was negative. However, 1.8% of women with a negative screen history before the age of 50 had dyskaryosis detected after the age of 50 during a median duration of follow-up of 33.2 months.

Four screening techniques based on visual inspection have been assessed for early detection of cervical neoplasia, mostly in low-resource settings:

- Unaided visual inspection (also-known as downstaging)
- Visual inspection with 3–5% acetic acid (VIA)
- Visual inspection with 3205% acid using low-level magnification (VIAM)
- Visual inspection with Lugol's iodine (VILI)

Unaided visual inspection involves naked-eye visualization of the cervix, without application of 3205% acid, to identify abnormal tissue harbouring cervical neoplasia, particularly inva-

rates of lesions among screened women were 5.8% for CIN 1, 0.7% fo CIN 2–3 and 0.2 for invasive cancer. 71% of women with CIN 1 and 80% of those with CIN 2–3 lesions accepted cryotherapy provided by nurses and excisional treatment by mid-level all,xcisional

ment in the Osmanabad trial; with cytology, the rate remained constant in the latter study. A high proportion of invasive cancers were diagnosed in stage I in women screened with VIA. The ultimate efficacy of VIA in reducing cancer incidence and mortality will become clearer with follow-up for cancer incidence and mortality in these studies.

An innovative option

VILI

in Uppsala, Sweden. Smears were available for up to 26 years before

Reference	Assay	Follow-up	Setting	Agence

re-screened before three years. Women with normal cytological results, but who are positive for high-risk HPV DNA, are at relatively low risk of having high-grade cervical neoplasia, and colposcopy should not be performed routinely in this setting.

	ThinPrep			SurePath		
Test threshold	estimate	95% CI	studies	estimate	95% CI	studies
HSIL+	1.72	1.42–2.08	21	1.47	1.14–1.89	7
LSIL+	1.74	1.47–2.06	21	1.52	1.24–1.86	7
LSIL	1.80	1.52–2.12	21	1.54	1.25–1.90	7
ASC+	1.23	1.07–1.40	19	1.19	0.96–1.46	7
ASC	0.95	0.84–1.09	19	0.93	0.67–1.31	7

et al

age group and by laboratory are shown in Table 70. There was no significant increase in the rates of HSIL when averaged across the three sites. However, in the ThinPrep laboratories, significantly more SIL and HSIL lesions were found, and one of them (lab C) also found more borderline lesions. In the laboratory where SurePath was used, less HSIL and borderline lesions were detected. The reason for this difference is not known. The increased identification of LSIL or worse lesions by SurePath was concentrated in the 20–34-year age group.

The reduction in inadequate rate should lead to fewer tests being performed, with a resulting decrease in workload for laboratories and primary care as well as recall systems. Referrals to colposcopy are likely to be affected only if the overall reporting of high-grade lesions increases. Comparing the running costs of LBC with those of conventional testing was complex since they utilize different amounts of laboratory resources.

There was some debate in the United Kingdom on the extent to which published differences between LBC and conventional cytology represented a true improvement (Herbert &

2002); a more recent article (Coste *et*

factory samples and a significant improvement in the identification of high-grade lesions (between 3 and 9 women per 1000 tested). Reduced workload and increased productivity were also demonstrated in laboratories.

In Ontario, Canada, SurePath was adopted for routine cervical screening in large screening laboratories in 2001, after training of large numbers of cytotechnologists. Almost one million routine cervical screening results were reviewed using the Ontario Provincial database. The results for 445 011 SurePath samples reported between January and June 2002 were compared with 445 225 conventional smear results from the same period in 2001 (Colgan *et al.,* 2004; McLachlin *et al.,* 2004). All slides had been screened manually. The SurePath cases showed 21% higher ofn
21% s(c21%) TjEMC/CREOOo114 BMC(in) TjEMC/C
ectivity and

Use of liquid-based

review method. Cytotechnicians were able to double their daily work output while maintaining the same quality (Biscotti

(OR = 1.66 per 50 cell increase,

Chapter 5

From the late 1960s, a decrease was seen in both the incidence of and mortality from cervical cancer in Finland, Sweden, Iceland and Denmark (Figure 54). The decrease, relative to the levels before screening, was largest in Finland, where the age-standardized mortality rate decreased more than 80% from 6.6 deaths per 100 000 in early 1960s to 1.2 deaths per 100 000 in the early 1990s (decrease 82%)

1960–88 and 7% since then (Sasieni *et al.,* 1995).

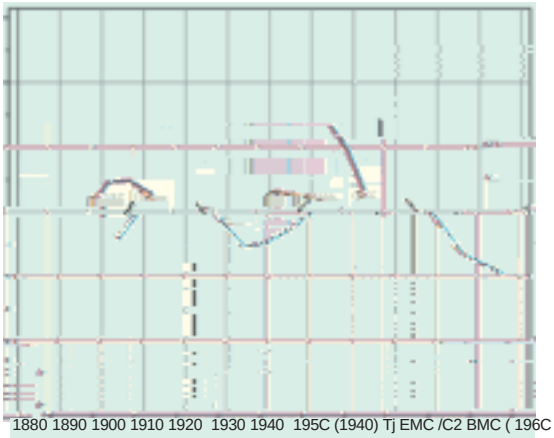
Coding of deaths as due to cancer of the uterus NOS has been common in many countries and this affpayv294.8T8rtimey.

Latin America

In contrast to most developed countries, mortality due to cervical cancer in Latin America increased between 1975 and 1985 (Restrepo *et al.*, 1993). A later analysis (Robles *et al.*, 1996) showed almost no significant downward change in mortality in Latin American countries between 1960 and 1993.

Figure 63 shows trends in age-

(Taucher *et al.*, 1996; Sankarana-
rayanan *et al.*



1880 1890 1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000
Birth cohort/period

1880 1890 1900 1910 1920 1930 1940 195C (1940) Tj EMC /C2 BMC (196C (1940) Tj EMC /C3 BMC

Statistical models have been developed to explore the effect of screening test, policy and programme characteristics on the expected reductions in incidence and mortality (and derivative quantities such as years of life saved). These have led to improved understanding of the relative importance of various screening

Most cervical cancer screening

tality rates and comparison of data in the screened population with what might have been seen in unscreened populations (Day, 1986).

Follow-up and treatment of abnormalities

Sasieni *et al.* (1996) calculated that in

assessment of coverage; a quality control system; and treatment for test-positive women. The means of achieving these, e.g., population registers or geographical location to define the population; personal invitation letters (call/recall) or mass education to invite women to participate; population-linked cervical cancer registry or sample surveys to assess coverage) will depend on the local circumstances.

The recognie -3Catne t eft fitiv vi "isto ettn..
Thproposurv

meets all the criteria outlined by Hakama *et al.* (1985). Although it may not be feasible to adopt all these elements of organized screening, many jurisdictions have incorporated some

interval. Participation should be evaluated according to age group, geography and other locally relevant indicators (e.g., health-care provider, ethnicity).

The effect of participation in reducing mortality and

screened, as opposed to number

requirement for three visits for women with abnormal cytological results, whereas for screening by visual inspection a one-visit strategy was modelled, and for HPV testing two visits. A substantial loss when women are required to return after the initial screening visit is observed in many developing countries, and this has an important effect on the cost-effectiveness of cytology, and to a lesser extent of HPV testing. When the authors modelled the effect of a limited number of tests in a lifetime, three tests at five-y

Ca 6
Summary of data

Incidence and mortality world-wide

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

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.

women. The median duration of a prevalently-detected HPV infection is typically about a year for high-risktypes 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 transientHPV infections will develop cytological abnormalities. When HPV is activelyreplicating in cells, it can produce char-

material for additional molecular testing, and a statistically significant

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-effec-

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

Delivery and uptake of screening

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

Chapter 7
Evaluation

screening should begin at a younger age in HIV-positive women is unclear and requires study.

Conventional cytology

The issues identified by the Working Group for implementation of conventional cytology were the ages at which

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Glossary

Cells that are considered suggestive but not diagnostic of a squamous intraepithelial lesion, at cytology.

The cervical cancer incidence rate expected in the absence of screening. It is not directly observable but estimated from the incidence in the target population before screening started (and adjusted for trend) or incidence at about the same time in an unscreened referent population, or in unscreened controls in the case of a randomized

addresses, at the beginning of each publication. Each participant serves as an independent scientist and not as a representative of any organization, government or industry. They are expected to put aside any stake they may have in a particular outcome and to evaluate the evidence objectively and with scientific rigour. All participants are required to complete a form before the meeting on which they declare any potential conflict of interest, due for example to recent links with commercial or industrial bodies that have a stake in the outcome of the

screening tests and screening procedures, i.e. the test itself and the way in which it is administered. The two merit separate, detailed evaluation. Each of the screening