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Randomised Evaluation of New Technologies within the Population-Based Cervical Cancer Screening Programme in Finland: Cross-Sectional Performance and Validity

Academic dissertation

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To my family

Abstract

A randomised and population-based screening design with new screening technologies has been applied to the organised cervical cancer screening programme in Finland. In this experiment the women invited to routine five-yearly screening are individually randomised to be screened with automation-assisted cytology, primary HPV DNA test or conventional cytology. By using the randomised design, the ultimate aim is to assess and compare the long-term outcomes of the different screening regimens.

The primary aim of the current study was to evaluate, based on the material collected during the implementation phase of the Finnish randomised screening experiment, the cross-sectional performance and validity of automation-assisted cytology and primary HPV DNA testing within service screening, in comparison to conventional cytology. The parameters of interest were test positivity rate, histological detection rate, relative sensitivity, relative specificity and positive predictive value. Relative sensitivity, relative specificity and positive predictive values were estimated with several cutoffs for test positivity and histological detection. Also, the effect of variation in performance by screening laboratory on age-adjusted cervical cancer incidence was assessed.

Based on the cross-sectional results, almost no differences were observed in the performance of conventional and automation-assisted screening, whereas primary HPV screening found more CIN lesions than conventional screening. However, with HPV screening the increase in CIN detection was mainly due to overrepresentation of mild- and moderate-grade lesions, which is likely to result in overtreatment since a great deal of these lesions would never progress to invasive cancer. Again, primary screening with an HPV DNA test alone caused substantial loss in specificity in comparison to cytological screening. With the use of cytology triage test, the specificity of HPV screening improved close to the level of conventional cytology. The specificity of primary HPV screening was also increased by increasing the test positivity cutoff from the level recommended for clinical use, but the increase was more modest than the one gained with the use of cytology triage.

The performance of a cervical cancer screening programme varied widely between the screening laboratories, but the variation in overall programme effectiveness between respective laboratory areas was more marginal and remained virtually constant from the very beginning of the organised screening activity. Thus, conclusive interpretations on the quality or success of screening should not be based on performance parameters only. In the evaluation of cervical cancer screening the outcome should be selected as closely as possible to the true measure of programme effectiveness, which is the number of invasive cervical cancers and subsequent deaths prevented in the target population.

Overall, in population-based screening, the new technologies studied have shown cross-sectional sensitivities and specificities reasonably close to conventional screening. Thus, provided the evaluation of screening effectiveness and adverse effects is systematically organised, they both can be used as primary tests in cervical cancer screening.

In general, new screening technologies are not necessarily any more effective than conventional cytology when used for population-based cervical cancer screening. Yet, the routine use of new technologies may lead to larger adverse effects compared to the conventional screening, if more follow-up recommendations are made or non-progressive lesions are detected and treated by increased numbers. Thus, the evaluation of benefits and adverse effects of each new suggested screening technology should be performed before the technology becomes an accepted routine in the existing screening programme. At best, the evaluation is performed randomised, within the population and screening programme in question, which makes the results directly applicable to routine use.

Tiivistelmä

Suomalaisen väestöpohjaisen kohdunkaulasyövän seulontaohjelman yhteydessä toteutetaan uusien seulontamenetelmien arviointia satunnaistetussa asetelmassa: viisivuotisseulontaan kutsuttavat naiset on satunnaistettu seulottavaksi automaatioavusteisella Papatestillä, papilloomavirustestillä (HPV-DNA-testi) tai perinteisellä Papatestillä. Arviointitutkimuksen perimmäisenä tarkoituksena on selvittää pitkäaikaisen seurannan myötä, kuinka vaikuttavaa kohdunkaulasyövän väestöseulonta eri menetelmillä on sekä osoittaa, onko satunnaistusryhmien välillä eroja.

Tämän väitöskirjatyön tavoitteena oli selvittää suomalaisen seulontamenetelmien arviointi-tutkimuksen aineistoa hyödyntäen, poikkileikkaustutkimuksen keinoin, automaatioavusteiseen Papatestiin ja papilloomavirustestiin perustuvien rutiiniseulontojen toimivuus (performance) ja osuvuus (validity) perinteiseen Papaseulontaan verrattuna. Toimivuutta ja osuvuutta tutkittiin satunnaishaaroissa laatumuuttujilla, joita olivat testipositiivisten määrä, löydösmäärät, suhteellinen herkkyys, suhteellinen tarkkuus ja positiivinen ennustearvo. Suhteellinen herkkyys ja tarkkuus sekä positiivinen ennustearvo laskettiin useaa testipositiivisuuden rajaa käyttäen useille eritasoisille löydöksille. Lisäksi väitöskirjatutkimuksessa selvitettiin seulontalaboratoriokohtaisesti, vaikuttavatko tutkituissa laatumuuttujissa havaitut erot kohdunkaulasyövän ilmaantuvuuteen.

Tutkimuksessa havaittiin, että automaatioavusteinen Papaseulonta oli käytännössä yhtä toimivaa kuin perinteinen Papaseulonta. Sen sijaan papilloomavirustestiin perustuvassa seulonnassa (HPV-seulonta) todettiin enemmän kohdunkaulasyövän esiasteita kuin perinteisessä seulonnassa; perinteisen Papaseulonnan perusteella todettuihin esiasteisiin nähden nämä esiasteet olivat kuitenkin useammin lieväasteisia. Koska lievät esiasteet paranevat usein itsestään, HPV-seulonta voi johtaa tarpeettomien hoitojen määrän lisääntymiseen. Tutkimuksessa havaittiin myös, että pelkkään papilloomavirustestiin perustuvan seulonnan tarkkuus oli merkittävästi heikompi kuin perinteisen Papaseulonnan, mutta kun Papatestiä hyödynnettiin HPV-DNA-testin ensimmäisenä varmistustestinä, HPV-seulonnan tarkkuus parani lähestulkoon perinteistä Papaseulontaa vastaavalle tasolle. Vaihtoehtoisesti HPV-seulonnan tarkkuutta voitiin parantaa nostamalla HPV-DNA-testipositiivisuuden raja-arvoa, mutta tällä tavalla tarkkuus parani vähemmän, kuin jos Papatestiä käytettiin papilloomavirustestin varmistustestinä.

Väitöskirjatutkimuksen perusteella kohdunkaulasyövän seulontaa toteuttavien laboratorioiden väliset erot laatumuuttujissa olivat suuria, kun taas kohdunkaulasyövän ilmaantuvuuden erot seulontalaboratorioita vastaavien alueiden välillä olivat varsin vähäisiä koko seulontaohjelman toiminta-aikana. Tämän vuoksi johtopäätöksiä kohdunkaulasyövän seulonnan laadusta ei pitäisi tehdä yksinomaan toimivuutta ja osuvuutta kuvaavien muuttujien perusteella, vaan laatu tulisi pyrkiä mittaamaan ensisijaisesti seulonnan vaikuttavuuden eli kohdeväestössä havaittujen kohdunkaulasyöpätapausten ja –kuolemien avulla.

Kokonaisuutena tutkittujen seulontamenetelmien herkkyys ja tarkkuus väestöpohjaisessa seulonnassa osoittautuivat kohtuullisen samantasoisiksi perinteisen Papaseulonnan kanssa. Näin ollen, mikäli seulonnan vaikuttavuuden ja haittavaikutusten arviointi on riittävästi järjestetty, näitä seulontamenetelmiä voidaan käyttää ensisijaisena seulontatestinä kohdunkaulasyövän väestöseulonnassa.

Yleisesti ottaen väestöpohjainen kohdunkaulasyövän seulonta uusilla seulontatesteillä ei välttämättä ole vaikuttavampaa kuin perinteinen Papaseulonta. Uusien seulontamenetelmien käyttöönotto voi kuitenkin johtaa seulonnan haittavaikutusten lisääntymiseen, jos aikaisempaa useammalle suositellaan seurantanäytettä tai lieviä esiasteita todetaan ja hoidetaan enemmän kuin perinteisellä seulonnalla. Tämän vuoksi uusien seulontamenetelmien hyöty- ja haittavaikutukset tulisi arvioida ennen niiden pysyvää käyttöönottoa rutiiniseulonnassa. Kun arviointi toteutetaan tieteellisin menetelmin siinä väestössä ja seulontaohjelmassa, jossa seulontamenetelmän käyttöönottoa harkitaan, tulokset ovat luotettavia ja sovellettavissa käytäntöön sellaisinaan.

Contents

Glossary of terms

Background incidence	Incidence in the target population in the absence of screening.
Detection rate	The number of histologically confirmed lesions detected at screening per persons screened.
Detectable preclinical phase (DPCP)	The period between the time at which a tumour becomes detectable with screening and the time it would become clinically detected.
Effect of screening	The result of screening. Refers either to the screening efficacy or effectiveness, depending on the screening setting.
Effectiveness of screening	The reduction in mortality of cancer (or, for cervical cancer only, in incidence of the invasive disease) in the target population of routine screening.
Efficacy of screening	The reduction in mortality and/or incidence observed under ideal conditions.
Incidence rate	The rate at which new cases occur in a population. Calculated as the number of new cases per person-years at risk.
Interval cancer	An invasive cancer diagnosed after a negative screening result, but before the subsequent screening or, in the absence of the subsequent screening, within a period equal to a screening interval.
Interval cancer rate	The number of interval cancers divided by person-years accumulated by persons with a negative screening result up to the subsequent screening or, in the absence of the subsequent screening, within a period equal to a screening interval.
Lead time	The period between the time a tumour was detected with screening and the time it, in the absence of screening, would have become clinically detected.
Length bias	The bias related to the fact that screening is more likely to detect cancers with long DPCPs and, thus, better prognosis than cancers with short DPCPs.

Mortality rate	The rate at which deaths occur in a population. Calculated as the number of deaths per person-years at risk.
Overdiagnosis	Detection by screening of lesions that would never have progressed to a clinical cancer during a lifetime.
Overtreatment	Treatment of screen-detected lesions that would never have progressed to a clinical cancer during a lifetime.
Participation rate	The number of screened as a proportion of all those invited to screening.
Performance	Execution of screening. Measured for monitoring purposes through various parameters of process, such as coverage rate, attendance rate, test positivity rate, histological detection rate, sensitivity and specificity.
Positive predictive value	The proportion of positive screening tests leading to a diagnosis of a histologically confirmed lesion among all the positive screening tests.
Screening interval	The defined interval between routine screenings within a screening programme.
Sensitivity of test	The proportion of those with positive test result among all the diseased.
Specificity of test	The proportion of those with negative test result among all the non-diseased.
Target population	The persons residing in an area covered by a screening programme and targeted by the programme, e.g. on the basis of age and sex.
Validity	The extent to which screening is capable of achieving what it is meant to achieve. Measured through various parameters, such as sensitivity, specificity, positive predictive value and negative predictive value.
Verification bias	Bias in the estimated diagnostic validity of a test that results from test positives and negatives verified with the gold standard in different fractions.

Abbreviations

ADC	Adenocarcinoma
AGC-FN	Atypical glandular cells, favour neoplasia
AGC-NOS	Atypical glandular cells, not otherwise specified
AIS	Adenocarcinoma *in situ*
ASC-US	Atypical squamous cells of undetermined significance
ASC-US+	Atypical squamous cells of undetermined significance or worse
ASC-H	Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion
BMD+	Borderline or mild dysplasia or worse
Ca	Carcinoma
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CIN 1	Cervical intraepithelial neoplasia grade 1
CIN 2	Cervical intraepithelial neoplasia grade 2
CIN 3	Cervical intraepithelial neoplasia grade 3
CIN 1+	Cervical intraepithelial neoplasia grade 1 or more severe lesion
CIN 2+	Cervical intraepithelial neoplasia grade 2 or more severe lesion
CIN 3+	Cervical intraepithelial neoplasia grade 3 or more severe lesion
CIS	Squamous-cell carcinoma *in situ*
GP5+/6+	Consensus primer pair used for PCR-based detection of HPV DNA
DNA	Deoxyribonucleic acid
DPCP	Detectable preclinical phase
E6	Human papillomavirus gene early 6
E7	Human papillomavirus gene early 7
FIGO	International Federation of Gynaecology and Obstetrics
FCO	Finnish Cancer Organisations
FDA	Food and Drug Administration
GIN	Glandular intraepithelial neoplasia
HC 2	Hybrid capture 2
HIV	Human immunodeficiency virus
HPV	Human papillomavirus

HSIL	High-grade squamous intraepithelial lesion
IARC	International Agency for Research on Cancer
ICD-10	International Statistical Classification of Disease and Related Health Problems, revision 10
L1	Human papillomavirus gene late 1
LBC	Liquid-based cytology
LSIL	Low-grade squamous intraepithelial lesion
LSIL+	Low-grade squamous intraepithelial lesion or worse
MY09/11	Degenerate primers used for PCR-based detection of HPV DNA
OR	Odds ratio
Pap	Papanicolaou
PCR	Polymerase chain reaction
PPV	Positive predictive value
RCT	Randomised controlled trial
Rlu	Relative light units
RNA	Ribonucleic acid
RR	Relative risk
RR_{crude}	Unadjusted i.e. crude relative risk
RR_{adj}	Adjusted relative risk
SCC	Squamous-cell carcinoma
Se	Sensitivity
Sp	Specificity
TBS	The Bethesda System
TBS 2001	The Bethesda System, version updated in 2001
VCE smear	Cervical smear consisting of vaginal, cervical and endocervical subsamples
VIA	Visual inspection with acetetic acid
VILI	Visual inspection with Lugol´s iodine
WHO	World Health Organisation

List of original publications

This thesis is based on the following articles referred to in the text by their Roman numerals.

I Nieminen P, Kotaniemi L, Hakama M, Tarkkanen J, Martikainen J, Toivonen T, Ikkala J, Luostarinen T, Anttila A. A randomised public-health trial on automation-assisted screening for cervical cancer in Finland: Performance with 470,000 invitations. Int J Cancer 2005;115:307-11.

II Nieminen P, Kotaniemi-Talonen L, Hakama M, Tarkkanen J, Martikainen J, Toivonen T, Ikkala J, Anttila A. Randomized evaluation trial on automation-assisted screening for cervical cancer: results after 777,000 invitations. J Med Screen 2007;14:23-8.

III Kotaniemi-Talonen L, Nieminen P, Anttila A, Hakama M. Routine cervical screening with primary HPV testing and cytology triage protocol in a randomised setting. Br J Cancer 2005;93:862-7.

IV Kotaniemi-Talonen L, Anttila A, Malila N, Tarkkanen J, Laurila P, Hakama M, Nieminen P. Screening with a primary human papillomavirus test does not increase detection of cervical cancer and intraepithelial neoplasia 3. Eur J Cancer 2008;44:565-571.

V Kotaniemi-Talonen L, Malila N, Nieminen P, Anttila A, Tarkkanen J, Laurila P, Hakama M. Test positivity cutoff level of a high risk human papillomavirus test could be increased in routine cervical cancer screening. Int J Cancer 2008;123:2902-2906.

VI Kotaniemi-Talonen L, Nieminen P, Hakama M, Seppänen J, Ikkala J, Martikainen J, Tarkkanen J, Toivonen T, Anttila A. Significant variation in performance does not reflect the effectiveness of the cervical cancer screening programme in Finland. Eur J Cancer 2007;43:169-74.

1. Introduction

Population-based screening for cervical cancer with a conventional cytological smear, a Papanicolaou smear, has been one of the greatest success stories in the history of cancer prevention. In countries like Finland with a well-established organised screening programme run since 1960s, the burden of cervical cancer has decreased tremendously from the time before screening, when it was one of the most common cancers of women (International Agency for Research on Cancer 2005). The decrease in cervical cancer incidence and mortality has been most marked with programmes that have achieved high screening coverage within the target population. Yet, in many if not most countries in the world, organisation or even implementation of a population-based screening programme has failed and the quality of screening activities and diagnostic procedures are not properly monitored. Thus, cervical cancer remains a major problem worldwide (Ferlay *et al.* 2004).

From the 1990s, the population-level effectiveness of the Finnish cervical cancer screening programme has remained quite stable (Finnish Cancer Registry 2007). However, among the youngest targeted age groups, i.e. women under 40 years, the effectiveness has decreased. Reasons for this phenomenon have primarily been looked for in the changed behaviour of the target population. It has been suggested that liberated sexual behaviour exposes women to sexually transmitted infections, including human papillomavirus infections, earlier and more often than before, which relates to increased cervical cancer risk. In addition, more women smoke tobacco, which increases the risks of cervical cancer and many other cancers. At the same time, the coverage of screening has remained low among young women.

Some interventions have been considered as potential solutions: to increase the screening coverage by administratory decisions, to campaign for screening or to send self-sampling tests to those who refuse screening; to integrate different primary or confirmatory tests into the existing screening programme; and to campaign against smoking, for condom use, and for a better understanding of factors related to sexual health. However, whether the effectiveness of our organised cervical cancer screening programme can be increased by any of these means, remains yet to be solved.

Since the launch of the first cytological screening programmes, the world has undergone huge technological and economic changes, which have affected the health care systems as well. Sophisticated technological innovations have become an inseparable part of modern health care in wealthy developed countries. Small medical companies have fused into multinational corporations that competitively introduce new commercial products and aggressively market them while looking for profit. In this overabundance, it has become a great challenge to governments to bear the costs of health care. Thus, prioritising and focusing on evidence-based medical practices has become essentially important; the key point is to make the most out of the limited resources available.

Currently, a growing number of adolescent girls are vaccinated against human papillomavirus infections in many developed countries in the hope of decreasing the burden of cervical cancer and other papillomavirus-related disease in the future. Despite the promising results on precancers from efficacy trials (The Future II Study Group 2007a, The Future II Study Group 2007b, Paavonen *et al.* 2007), the long-term effectiveness and cost-effectiveness of papillomavirus vaccinations has not been assessed. While the evaluation is ongoing, screening still remains the primary method for cervical cancer prevention.

The objective of this work was to study from the public health perspective the impacts of selected new technologies, automation-assisted cytology and human papillomavirus testing on a cervical cancer screening programme. We were interested to discover how well these technologies perform within the routine screening programme incorporated as primary tests in comparison to conventional cytological screening and whether we should consider changing the primary screening test of the organised cervical cancer screening programme in Finland. The work is based on a large randomised evaluation trial run within the population-based cervical cancer screening in Finland. This trial is designed to produce solid evidence-based information on the new technologies studied as they are routinely used and, thus, the results are directly applicable into practice.

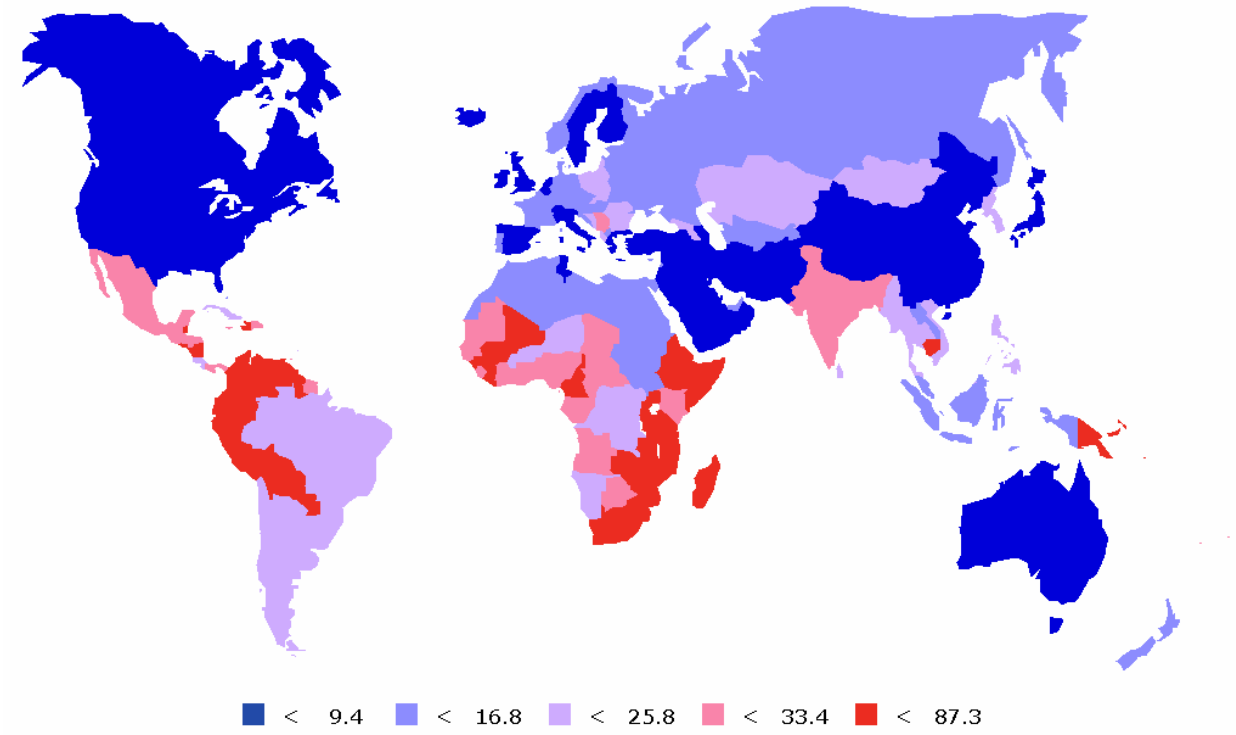
2. Review of the literature

2.1. Biology and epidemiology of cervical cancer

2.1.1. Incidence and mortality

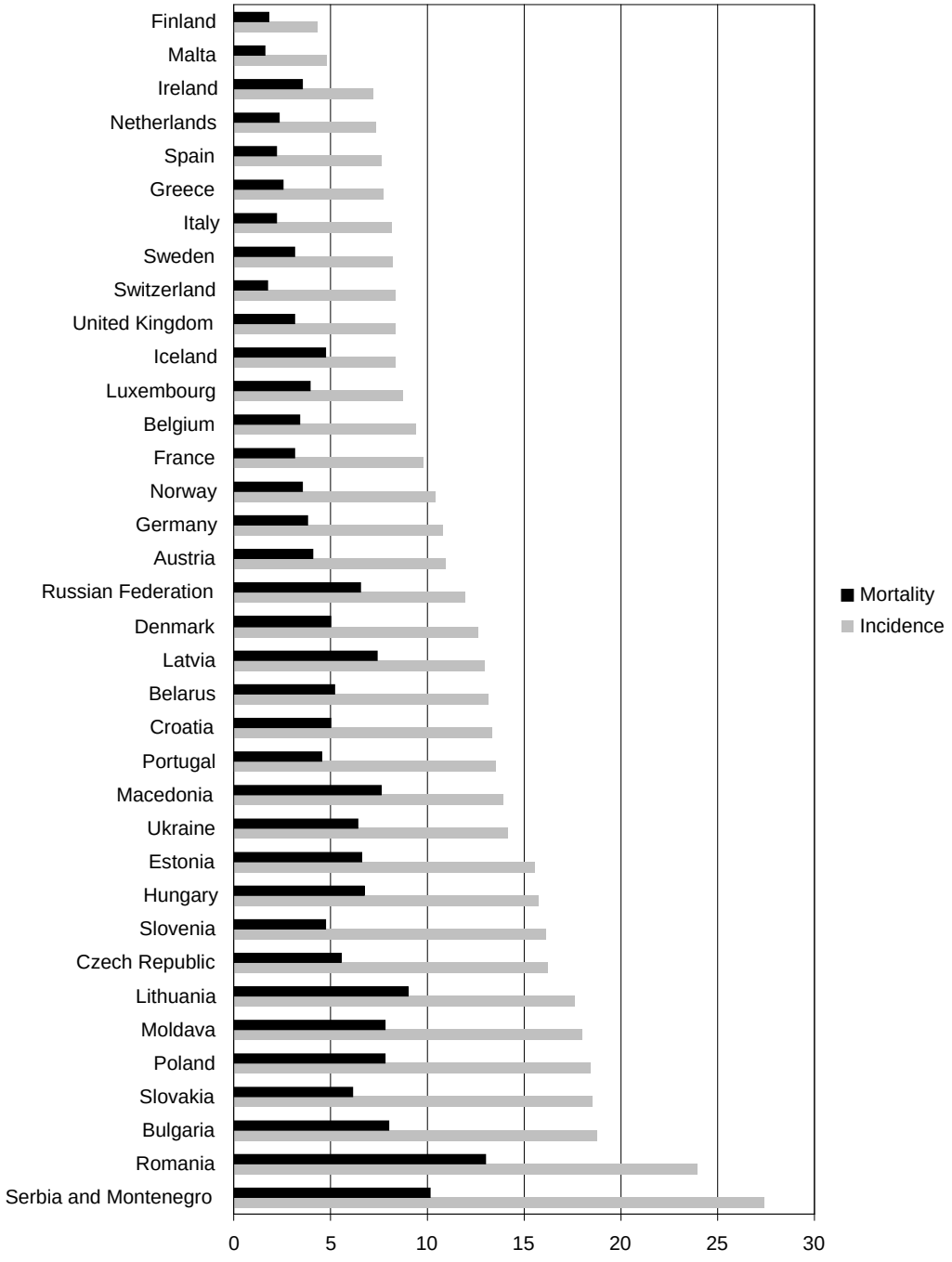
Cancer of the uterine cervix (or cervical cancer) is the second most common cancer and the third most common cause of cancer deaths among women worldwide (Ferlay *et al.* 2004, International Agency for Research on Cancer 2005). In the year 2002, an estimated 493,000 new invasive cervical cancer cases were diagnosed and 274,000 cervical cancer deaths occurred in the world. The burden of cervical cancer is particularly high is the less developed regions of the world, where more than 80% of invasive cervical cancers are diagnosed (Ferlay *et al.* 2004). The highest incidence rates (number of incident cases of invasive cancer/ 100,000 women/ year) are observed in Central and Southern America, the Caribbean, sub-Saharan Africa, and South and South-East Asia (Figure 1) (Ferlay *et al.* 2004, International Agency for Research on Cancer 2005).

Figure 1 Age-standardised (world standard population) incidence of invasive cervical cancer in the world per 100,000 women, from Ferlay *et al.* 2004



In Europe, an estimated 34,300 women were diagnosed with cervical cancer in the 27 member states of the European Union (EU) in the year 2004 and about 16,300 deaths from the disease occurred (Boyle and Ferlay 2005, Arbyn *et al.* 2007). The highest European incidence rates are observed in some Eastern and Central European countries (Figure 2).

Figure 2 Age-standardised (world standard population) cervical cancer incidence and mortality in European countries per 100,000 women



Data adapted from Ferlay *et al.* 2004. For Albania and Bosnia Herzegovina original data were not available.

In Finland, cervical cancer was the 19th most common cancer among women in the year 2005 with 125 newly diagnosed cases. During the last decade, approximately 160 women have been annually diagnosed with invasive cervical cancer in Finland, and about 60 related deaths have been registered (Finnish Cancer Registry 2007). Compared to most countries of the world, the rates of cervical cancer incidence and mortality (number of cancer deaths/ 100,000 women/ year) in Finland are very low, resulting from long-term cervical cancer prevention with a population-based screening programme (Anttila *et al.* 2008).

The unequal worldwide distribution of cervical cancer cases is a relatively new phenomenon, as before the first population-based screening programmes were introduced in the 1960s and 1970s the incidence in most of Europe, North America and Japan was similar to that observed in many less developed countries today (Gustafsson *et al.* 1997a).

Differing from many other cancers, cervical cancer primarily affects fertile-aged women: most cases appear between the ages 35 and 50 (Gustafsson *et al.* 1997b). As the relative 5-year survival rate of cervical cancer patients is approximately 60% (Arbyn *et al.* 2008a), the disease can be considered as a major cause of morbidity and mortality among working-aged women.

2.1.2. Pathology

Based on their cellular origin, cancers of the cervix uteri are divided into multiple histological classes (Table 1). The vast majority of cervical cancer cases originate from epithelial tissue, i.e. they are carcinomas. Squamocellular carcinoma is the most common type, adenocarcinoma being the second most common. In areas with low cervical cancer incidence due to cervical screening, the proportion of adenocarcinomas is higher than the average (International Agency for Research on Cancer 2005). In Finland, 46 (36.8%) of the total 125 cervical cancers diagnosed in 2005 were adenocarcinomas.

Table 1 World Health Organisation (WHO) histological classification of tumours of the uterine cervix, from International Agency for Research on Cancer 2005

- **Epithelial tumours**
  - Squamous tumours and precursors
    - Squamous cell carcinoma
      - Keratinizing
      - Non-keratinizing
      - Basaloid
      - Verrucous
      - Warty
      - Papillary
      - Lymphoepithelioma-like
      - Squamotransitional
    - Early invasive (microinvasive) squamous cell carcinoma
    - Squamous intraepithelial neoplasia
      - Cervical intraepithelial neoplasia grade 3 /
      - Squamous cell carcinoma *in situ*
    - Benign squamous cell lesions
      - Condyloma acuminatum
      - Squamous papilloma
      - Fibroepithelial polyp
  - Glandular tumours and precursors
    - Adenocarcinoma
      - Mucinous adenocarcinoma
        - Endocervical
        - Intestinal
        - Signet-ring cell
        - Minimal deviation
        - Villoglandular
      - Endometroid adenocarcinoma
      - Clear cell adenocarcinoma
      - Serous adenocarcinoma
      - Mesonephric adenocarcinoma
    - Early invasive (microinvasive) adenocarcinoma
    - Adenocarcinoma *in situ*
    - Glandular dysplasia
    - Benign glandular lesions
      - Müllerian papilloma
      - Endocervical polyp
  - Other epithelial tumours
    - Adenosquamous carcinoma
      - Glassy cell carcinoma variant
    - Adenoid cystic carcinoma
    - Adenoid basal carcinoma
    - Neuroendocrine tumours
      - Carcinoid
      - Atypical carcinoid
      - Small cell carcinoma
      - Large cell carcinoma
  - Undifferentiated carcinoma

- **Mesenchymal tumours and tumour-like conditions**
  - Leiomyosarcoma
  - Endometroid stromal sarcoma, low-grade
  - Undifferentiated endocervical sarcoma

Table 1 Continued

Mesenchymal tumours and tumour-like conditions, continued
Sarcoma botryoides
Alveolar soft part sarcoma
Angiosarcoma
Malignant peripheral nerve sheath tumour
Leiomyoma
Genital rhabdomyoma
Postoperative spindle cell nodule
Mixed epithelial and mesenchymal tumours
Carcinosarcoma (malignant Müllerian mixed tumour, metaplastic carcinoma)
Adenosarcoma
Wilms tumour
Adenofibroma
Adenomyoma
Melanocytic tumours
Malignant melanoma
Nevus cell nevus
Miscellaneous tumours
Tumours of germ cell type
Yolk sac tumour
Dermoid cyst
Mature cystic teratoma
Lymphoid and haematopoietic tumours
Malignant lymphoma
Leukemia
Secondary tumours

Biologically, the epithelial tissue of the uterine cervix derives from two distinctive embryological sources: the non-keratinized stratified squamous epithelium lining the ectocervix (or portio) derives from the urogenital sinus, whereas the mucus-secreting columnar epithelium covering the endocervical canal is of Müllerian origin (International Agency for Research on Cancer 2005). The junction between these two epithelia, the squamocolumnar junction, is not anatomically fixed, but it migrates throughout life. After puberty, this migration mainly occurs through a process called squamous metaplasia, in which the columnar epithelium is gradually replaced by stratified epithelium. The area of the cervix where the metaplastic process takes place, the transformation zone, is the area where most squamous-cell carcinomas develop. Adenocarcinomas primarily develop within the endocervical canal, often near the squamocolumnar junction.

2.1.3. Aetiology

Oncogenic human papillomavirus types

Based on the current knowledge, both squamous and adenomatous cervical cancers are caused by specific human papillomaviruses (HPV) (zur Hausen 1976, Colgan and Lickrish 1990, Duggan *et al.* 1994, Bosch *et al.* 1995, Ursin *et al.* 1996, Denehy *et al.* 1997, Walboomers *et al.* 1999, Bosch *et al.* 2002, Muñoz *et al.* 2003). Human papillomaviruses are small, non-enveloped, double-stranded DNA viruses that infect differentiating epithelial cells of the skin and mucosa (International Agency for Research on Cancer 2007). Based on the DNA sequence of the most conserved region of HPV genome, open reading frame (ORF) of the major structural protein late 1 (L1), human papillomaviruses are divided into types (homology difference more than 10% to the closest known type), sub-types (difference 2-10%) and variations (difference less than 2%) (de Villiers *et al.* 2004, International Agency for Research on Cancer 2007). Up to the date, more than 130 HPV types have been identified (International Agency for Research on Cancer 2005, Dillner *et al.* 2008b).

About 40 HPV types may infect anogenital area (de Villiers *et al.* 2004). Based on their oncogenic potential, these 40 types are generally divided into low-risk types, which are mainly detected in genital warts and mild dysplasia (or cervical intraepithelial neoplasia (CIN) grade 1, CIN 1), and high-risk types associated with the development of invasive cervical cancer. The most common high-risk HPV types identified in cervical cancers are, in order of decreasing prevalence, types 16, 18, 33, 45, 31, 58, 52, 35, 59, 56, 51, 39, 73, 68 and 82 (Clifford *et al.* 2003, Muñoz *et al.* 2003). Further three types, i.e. HPV 26, 53 and 66 are designated as probably high-risk (Muñoz *et al.* 2003). HPV 16 and 18 account for 70% of cervical cancers worldwide (Muñoz *et al.* 2004). HPV 16 is more often identified in squamous-cell carcinoma than in adenocarcinoma and HPV 18 more often in adenocarcinoma than in squamocellular carcinoma (Zielinski *et al.* 2003, International Agency for Research on Cancer 2005).

In benign, productive HPV infections where new viral particles are produced and released, HPV DNA remains episomal in host cells. In some cases, however, the HPV DNA integrates into the genome of the host cell. These integrated genomes are often detected in CIN grade 3 (CIN 3) and

cancer (Boshart *et al.* 1984, Schwarz *et al.* 1985, Yee *et al.* 1985). It has been suggested that the potential to become integrated into the DNA of the host cell would give certain growth advantage to the infected cells by activating the expression of viral oncogenes, in particular genes early 6 and 7 (E6 and E7) (Jeon *et al.* 1995, zur Hausen 2000). However, a number of studies have found only episomal DNA of HPV 16 in 20-70% of cervical cancers and in 75-97% or CIN 3 (Fuchs *et al.* 1989, Matsukura *et al.* 1989, Cullen *et al.* 1991, Pirami *et al.* 1997). Thus, the relation of HPV DNA integration to the cancerous process is yet unclear.

Sexual transmission is the predominant mode of anogenital HPV acquisition (Rylander *et al.* 1994, Franco *et al.* 1995, Bosch *et al.* 1996, Dillner *et al.* 1999, Kjaer *et al.* 2001, Sellors *et al.* 2003). Due to this, the most important risk factors for HPV infection are related to sexual behaviour. A person's large number of lifetime sexual partners and partners' partners increases the risk (Karlsson *et al.* 1995, Thomas *et al.* 1996, Castellsagué *et al.* 1997) as well as having the first sexual intercourse at a young age (Terris *et al.* 1967). Circumcision of the male partner seems to reduce the risk of cervical cancer among women (Castellsagué *et al.* 2002). Due to changes in sexual behaviour, the cervical cancer risk has recently increased among young women in many western populations (Anttila *et al.* 1999, Peto *et al.* 2004, Bray *et al.* 2005).

In addition to cervical cancer, oncogenic human papillomaviruses have also been associated with a number of other tumours, including more than 50% of cancers of anus, penis vulva and vagina, a proportion of oral and oropharyngeal cancers, and some skin cancers (International Agency for Research on Cancer 2007).

Co-factors

Even if high-risk HPV infection has such a strong causal association with the cancer of the cervix that it is considered necessary for the cancer development, it is not a sufficient cause of cancer, i.e. high-risk HPV infection does not necessarily lead to cervical cancer (Bosch *et al.* 2002). Apparently there are several exogenous and endogenous factors which together with a high-risk HPV infection increase the risk of cervical cancer development.

The best-known co-factor for cervical cancer development is exposure to tobacco smoke with a risk estimate of roughly 2.0 (Williams and Horm 1977, Winkelstein 1977, Burger *et al.* 1993, Ylitalo *et al.* 1999, Hildesheim *et al.* 2001, Lacey *et al.* 2001, Castle *et al.* 2002b, Castellsagué and Muñoz 2003, Plummer *et al.* 2003, Vaccarella *et al.* 2008). The use of oral contraceptives for at least five years has also been shown to increase cervical cancer risk (Smith *et al.* 2003). Based on a pooled analysis of 10 case-control studies, the number of full-term pregnancies is directly related to the increasing cervical cancer risk (Muñoz *et al.* 2002). The risk factors for adenocarcinoma are mostly the same as those for squamous cell type, except for smoking (Lacey *et al.* 2001, Berrington de Gonzalez *et al.* 2004).

Seroprevalence of antibodies to Chlamydia trachomatis has also been associated with the increased cervical cancer risk (Hakama *et al.* 2000, Koskela *et al.* 2000, Anttila *et al.* 2001, Wallin *et al.* 2002, Smith *et al.* 2004, Madeleine *et al.* 2007), as well as seroprevalence of herpes simplex virus type 2 antibodies (Smith *et al.* 2002), although many studies do not show any association. The association of many other infectious agents with cervical cancer has been studied but not confirmed (International Agency for Research on Cancer 2007). It has been suggested that cervical inflammation in general, regardless of the infectious agent, may be a risk factor for the progression of HPV infection (Castle and Giuliano 2003), which might partially explain the variable findings on co-infections.

Infection with human immunodeficiency virus (HIV) increases the risk of persistent high-risk HPV infection and the risk of progressive disease (Sun *et al.* 1995, Cappiello *et al.* 1997, Rezza *et al.* 1997, Sun *et al.* 1997, Maiman *et al.* 1998, Rugpao *et al.* 1998, Six *et al.* 1998, Massad *et al.* 1999, Cubie *et al.* 2000, Ellerbrock *et al.* 2000, Frisch *et al.* 2000, Duerr *et al.* 2001, Massad *et al.* 2001, Volkow *et al.* 2001, Chirenje *et al.* 2002, Hawes *et al.* 2003), especially if the count of CD4+ cells is low (Maiman *et al.* 1998, Six *et al.* 1998, Kapiga *et al.* 1999, Massad *et al.* 1999, Palefsky *et al.* 1999, Duerr *et al.* 2001, Hawes *et al.* 2003) or the viral load is high (Cubie *et al.* 2000, Heard *et al.* 2000). Highly active antiretroviral therapy has been shown to induce regression and to diminish the risk of progression (Heard *et al.* 2000, Minkoff *et al.* 2001, Ahdieh-Grant *et al.* 2004).

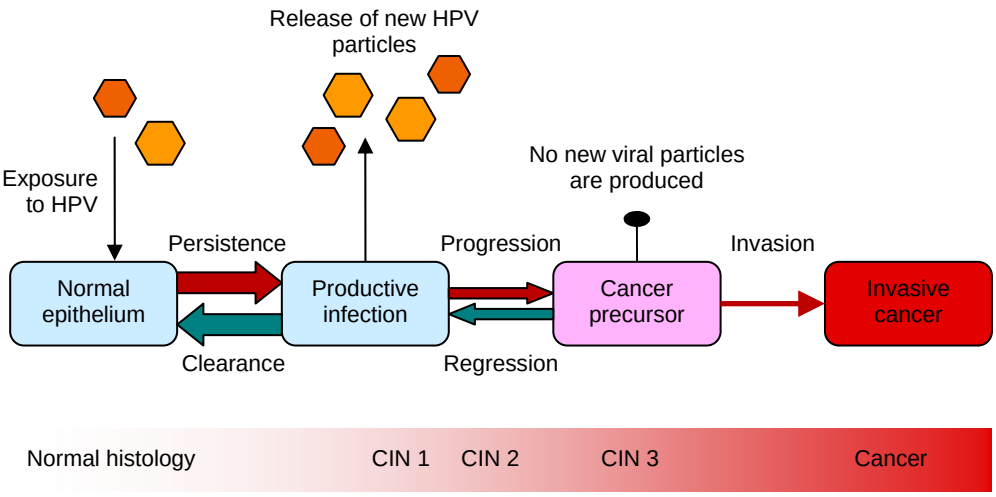
More generally, long-term immunosuppression seems to increase the risk of cervical cancer among other anogenital cancers: in a few population-based follow-up studies, the observed

incidence of cervical cancer among renal transplant patients has been higher than the expected rate (International Agency for Research on Cancer 2007). In a study conducted in Australia and New Zealand, the age-standardised incidence ratio in transplant recipients was 3.3 after a mean follow-up of 5.8 years, whereas, in comparison, it was 0.74 for dialysis patiens (Fairley *et al.* 1994). In a register-based study from the Nordic countries, the standardised incidence ratio for cervical cancer in transplant recipients was somewhat higher, 8.6 after an average of 4.8 years of follow-up (Birkeland *et al.* 1995). This study also showed that the most important determinant of increased cancer risk among transplant patients was age below 45 years at the time of transplantation supporting of the theory that an impaired immune system allows carcinogenic factors to act.

2.1.4. Natural history

The actual development of cervical cancer is a multi-step process, which is quite unclear yet. However, it is known that squamous-cell cervical cancer develops through precancerous stages (dysplastic lesions) that are preceded by a persistent infection with high-risk HPV (Figure 3) (Koutsky *et al.* 1992, Ho *et al.* 1995, Remmink *et al.* 1995, Ho *et al.* 1998b, Nobbenhuis *et al.* 1999, Wallin *et al.* 1999, Schlecht *et al.* 2001). Thus, cervical cancer is generally regarded as a rare long-term consequence of a common sexually transmitted infection with human papillomavirus.

Figure 3 Natural history of cervical cancer development

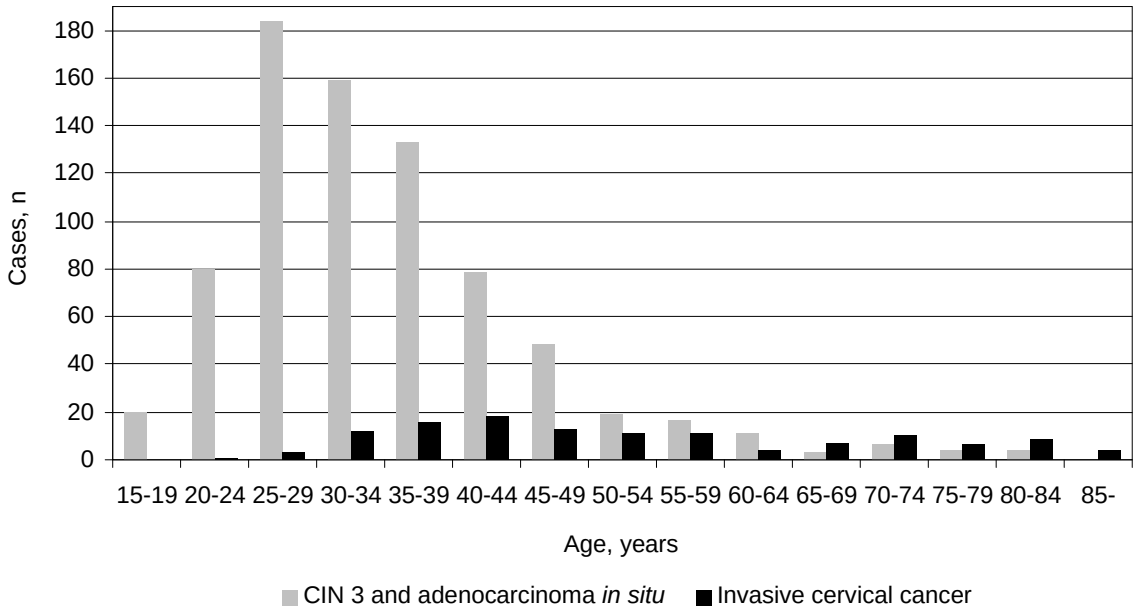


Abbreviations: HPV, human papillomavirus; CIN 1, cervical intraepithelial neoplasia grade 1; CIN 2, cervical intraepithelial neoplasia grade 2; CIN 3, cervical intraepithelial neoplasia grade 3

Infections with HPV types, both high-risk and low-risk, are relatively common at the population level but the overall HPV prevalence as well as HPV type distribution vary greatly between countries worldwide (Clifford *et al.* 2005, Franceschi *et al.* 2006, International Agency for Research on Cancer 2007). Usually the infection is first acquired at youth, within a few years from the sexual debut (Koutsky *et al.* 1992, Melkert *et al.* 1993, Hildesheim *et al.* 1994, Burk *et al.* 1996, Ho *et al.* 1998a, Woodman *et al.* 2001, Winer *et al.* 2003, Rodriguez *et al.* 2007). Most of the HPV infections are transient, i.e. they clear spontaneously within months or a few years at the most: an estimated 70% of the infections clear in 12 months (Hildesheim *et al.* 1994, Evander *et al.* 1995, Ho *et al.* 1998a, Franco *et al.* 1999, Molano *et al.* 2003, Richardson *et al.* 2003) and more than 90% will have cleared in 24 months (Ho *et al.* 1998a). However, the type of acquired HPV infection, individual differences in cell-mediated immune system and other host-related factors such as diet, smoking and co-existing sexually transmitted infections seem to have an impact on the length of persistence (Sun *et al.* 1997, Kjaer *et al.* 2002, Sedjo *et al.* 2002, Richardson *et al.* 2003, Bulkmans *et al.* 2007a). On average, infections with high-risk HPV types have been shown to last a couple of months longer than low-risk HPV infections (Franco *et al.* 1999, Giuliano *et al.* 2002, Richardson *et al.* 2003, Schlecht *et al.* 2003). However, in a long-term follow-up study by Schiffman *et al.* only HPV 16 was shown to persist longer than other HPV types (Schiffman *et al.* 2005). HPV infections have been suggested to persist longer as age increases (Hildesheim *et al.* 1994).

The prevalence of high-risk HPV infections is highest among 20- to 29-year-old women, from where it decreases and stabilises to the baseline level of 2-8% in women older than 35 years (Bosch *et al.* 1992, Muñoz *et al.* 1992, Parkin *et al.* 1997, Jacobs *et al.* 2000, Leinonen *et al.* 2008). In Finland, the prevalence of oncogenic HPV infections within the general population targeted by the organised screening programme (among women aged 25 to 65 years) is 7.5% (Leinonen *et al.* 2008). Following the prevalence peak of HPV infection, a peak in the incidence of cervical precancer is observed in about 7-10 years and, respectively, a peak in the invasive cervical cancer incidence in 20-25 years (Dunn and Martin 1967, International Agency for Research on Cancer 2007). In Finland, an estimated 80% of cervical cancer has been prevented by screening, and therefore the peak in invasive cervical cancer is not as obvious as in countries without effective screening (Figure 4).

Figure 4 Age-distribution of invasive cervical cancers and preinvasive lesions diagnosed in Finland in 2005 and registered at the Finnish Cancer Registry



Based on data derived from the main database of the Finnish Cancer Registry.

Precancerous cervical lesions can be divided into two categories based on their potential of progression: productive and self-limited infections (including histopathological classes of koilocytic atypia, koilocytosis, condyloma, mild dysplasia, CIN 1, low-grade squamous intraepithelial lesion (LSIL)) and potentially progressive precancerous lesions (moderate dysplasia, CIN grade 2 (CIN 2), severe dysplasia, CIN 3, carcinoma *in situ,* high-grade squamous intraepithelial lesion (HSIL)) (Wright *et al.* 2002a). Estimated rates of progression have varied depending on the endpoint used and the age of the women. In 1991, van Oortmarssen and Habbema published a model-based estimation that the progression rate of any CIN ranges from 16% among women aged 18 to 34 to 60% among women aged 35 or older (van Oortmarssen and Habbema 1991). In 1993, Östör conducted a pooled analysis of studies published between 1950 and 1992 and estimated that about 1% of CIN 1 lesions would develop into invasive cancer if left untreated, whereas an estimated 5% of CIN 2 lesions and approximately 12% of CIN 3 lesions would progress to invasion (Östör 1993); this has later been judged as an underestimate (International Agency for Research on Cancer 2005, Anttila *et al.* 2008). In a review by Mitchell *et al.* it was estimated that 36% of carcinoma *in situ* lesions are progressive (Mitchell *et al.* 1996). This rate is close to the early estimation by Hakama and Räsänen-Virtanen, which suggested a 28-39% progression rate for pre-

invasive cervical lesions (Hakama and Räsänen-Virtanen 1976). In 1999, Holowaty *et al.* estimated, that for mild, moderate and severe dysplasia the actuarial progression rates for carcinoma *in situ* or worse within 10 years are 2.8% (95% confidence interval (CI) 2.5-3.1%), 10.3% (95% CI 9.4-11.2%) and 20.7% (95% CI 17.0-24.3%), respectively; and for invasive cancer 0.4% (95% CI 0.3-0.5%), 1.2% (95% CI 0.9-1.5%) and 3.9% (95% CI 2.0-5.8%) (Holowaty *et al.* 1999). A new cohort study from New Zealand suggests higher progression rates for CIN 3 lesions: 20.0% (95% CI 13.7-28.7%) of the women with untreated CIN 3 developed a cancer of cervix or vaginal vault after 10 years, and 31.3% after 30 years (McCredie *et al.* 2008). Nevertheless, the duration of precancerous states is generally long with detectable carcinoma *in situ* preceding invasive cancer by at least 5 to 10 years (Kasper *et al.* 1970, Prorok 1986).

A significant proportion of CIN lesions regress on their own. Of CIN 1 lesions an estimated 57% are regressive, as well as 43% of CIN 2 and 32% of CIN 3 lesions (Östör 1993, Mitchell *et al.* 1996, Melnikow *et al.* 1998). In 1982, Boyes *et al.* suggested that the rate of regression for carcinoma *in situ* would be 40-60% (Boyes *et al.* 1982). The rate of regression is particularly high among women under 30 (Moscicki *et al.* 2004). HPV clearance is associated with CIN regression (Nobbenhuis *et al.* 2001a, Zielinski *et al.* 2001, Schiffman *et al.* 2002).

Differing from squamous-cell cervical cancer, the only well characterised precancerous stage of adenocarcinoma is adenocarcinoma *in situ* (International Agency for Research on Cancer 2005), the natural course of which is not fully understood (Krivak *et al.* 2001).

2.2. Diagnosis and treatment of cervical neoplasia

2.2.1. Exfoliative cytology

The basis of cervical cancer diagnostic is exfoliative cytology: a sample scraped from the cervical epithelium with a spatula, brush, broom, cotton swab or some special sampler tool and prepared for analysis. Exfoliative cytological sample is often used for cytopathological examination, where the processed sample is studied with light microscopy for cytomorphological abnormalities.

Furthermore, exfoliative cells may be used for other analyses, e.g. for high-risk HPV DNA detection.

Sampling and smear preparation

In Finland, the cytological sample of the cervix is traditionally used for a conventional Papanicolaou (Pap) smear. It consists of three subsamples – vaginal, cervical and endocervical samples (a VCE smear). For sample-taking, a women lies in the lithotomy position and the cervix is visualised by passing a speculum into the vagina. The sample-taker then collects the vaginal subsample from the vaginal fornices with the blunt end of an Ayre's spatula. The cervical sample is collected from the portio, primarily from the transformation zone, with the pointed end of the Ayre's spatula: the tip of the spatula is placed into the endocervical canal and the spatula is rotated 360° applying gentle pressure. Endocervical sampling is performed with an endocervical brush, which is rotated 180° in the endocervical canal. In the preparation of a conventional Pap smear, all the subsamples are placed on the same microscope slide of glass, which is then fixed, stained and covered with a cover glass.

Terminologies of cytopathological examination

Papanicolaou classification is the oldest terminology used for cytopathological examination. The original terminology divides cytological findings into five classes, ranging from normal to malignant: class I refers to absence of atypical cells (i.e. normal cytology); class II to atypical cytology with no evidence of malignancy; class III is suggestive of, but not conclusive for, malignancy; class IV is strongly suggestive of malignancy; and class V conclusive for malignancy (Papanicolaou 1954). In most of the world, newer terminologies have replaced the Papanicolaou classification in cervical cytology. However, a modified Papanicolaou classification including a descriptive diagnosis was used as the primary terminology in the Finnish cervical cancer screening programme up to 2005 (Finnish Cancer Registry 2007), and other modifications are still used in Germany (Munich classification) and the Netherlands (CISOE-A) (Hanselaar 2002, Petry *et al.* 2003, International Agency for Research on Cancer 2005).

Today, the Bethesda System (TBS) (Solomon *et al.* 2002) is the most widely used terminology for cytopathological examination of the cervix. It has been adopted in Finland, too, and since 2006, the reporting of the cervical smears from the Finnish organised screening programme has been based on TBS, although the Papanicolaou class is also reported. TBS was originally developed in 1988, but it has since been updated twice; the current version was revised in 2001. The most important features of TBS are that it includes descriptive diagnosis and evaluation of specimen adequacy and it separates intraepithelial atypia from infectious or reactive changes, which all are missing from the original Papanicolaou classification. The 2001 Bethesda System (TBS 2001) is described in Table 2, in comparison to other widely used terminologies (International Agency for Research on Cancer 2005, International Agency for Research on Cancer 2007, Arbyn *et al.* 2008a).

The World Health Organisation (WHO) terminology (Riotton *et al.* 1973), also known as the dysplasia terminology, enables a fairly direct correlation between cytopathologic and histopathologic findings. The deficits of this terminology are that it does not really have categories for benign conditions and it does not include the evaluation of specimen adequacy. The British Society for Clinical Cytology (BSCC) terminology is a modification of the WHO terminology. It has been recently updated, and therefore it is well compatible with TBS 2001 (Denton *et al.* 2008).

The CIN terminology (Richart 1968, 1973) was developed on the basis of the observation, that mild, moderate and severe precancerous lesions represent different stages of the same biological process, rather than separate entities. Like the WHO terminology, it does not deal with non-neoplastic conditions or specimen adequacy. It is only recommended for histopathology (Herbert *et al.* 2007).

Table 2 Terminologies of cytopathological examination

Papanicolaou	I	II		III			IV			V
TBS 2001	Negative for epithelial abnormality	ASC-US		LSIL		ASC-H	HSIL			Invasive SCC
		AGC-NOS				AGC-FN			AIS	Invasive ADC
WHO	Normal	Atypia		Mild dysplasia		Moderate dysplasia		Severe dysplasia	CIS	Invasive SCC
		Atypical glandular cells							AIS	Invasive ADC
CIN	Normal	Atypia		Condyloma	CIN 1	CIN 2		CIN 3		Invasive SCC
		Atypical glandular cells							GIN	Invasive ADC

Abbreviations: TBS 2001, The Bethesda System version 2001; WHO, World Health Organization; CIN, cervical intraepithelial neoplasia; ASC-US, Atypical squamous cells of undetermined significance; ASC-H, Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; HSIL, High-grade squamous intraepithelial lesion; SCC, Squamous-cell carcinoma; AGC-NOS, atypical glandular cells , not otherwise specified; AGC-FN, Atypical glandular cells, favour neoplasia; AIS, Adenocarcinoma *in situ*; ADC, adenocarcinoma; CIS, squamous-cell carcinoma *in situ*; CIN 1, cervical intraepithelial neoplasia grade 1; CIN 2, cervical intraepithelial neoplasia grade 2; CIN 3, cervical intraepithelial neoplasia grade 3; GIN, glandular intraepithelial neoplasia

Management

Worldwide, women with high-grade cytological lesions (roughly equal to Pap class III-V in Papanicolaou classification system; ASC-H, HSIL or squamous-cell cancer in TBS 2001) are referred for diagnostic colposcopy for confirmation (Melnikow *et al.* 1998, Wright *et al.* 2002b). The appropriate management of women with minor cytological lesions (Pap class II; ASC-US and LSIL) is, instead, unclear (Wright *et al.* 2002b, International Agency for Research on Cancer 2005). Recommendations for management vary between countries from conservative follow-up with repeat cytology or triage with an HPV DNA test to immediate colposcopy referral (International Agency for Research on Cancer 2005, Arbyn *et al.* 2008a). Nevertheless, women with minor cytological lesions are undoubtedly at increased risk of CIN 3 or cancer (Viikki *et al.* 2000a, Arbyn *et al.* 2004, Arbyn *et al.* 2005), which necessarily calls for some form of management.

In Finland, national recommendations for management of cytopathological and histopathological changes in the cervix, vagina and vulva are given by the Finnish Medical Society Duodecim (Finnish Current Care guidelines 2006). Based on these recommendations, ASC-US result is an indication for a new cervical smear after 6 to 12 months, and colposcopy is indicated only after recurrent (2 to 3 times) ASC-US finding over 12 to 24 months (Melnikow *et al.* 1998). Women of screening age with LSIL or more severe lesion are directed to colposcopy. Colposcopies are to be performed at least within six months; the recommended time frame dependens on the severity of the cytological lesion.

2.2.2. Colposcopy

Generally, the screening test is not intended to be diagnostic. Instead, the diagnostic confirmation is made with another test. In the case of suspected cervical neoplasia, the diagnostic test of the art is colposcopy, examination of the uterine cervix, vagina and vulva with a colposcope, i.e. a special binocular light microscope with 6- to 40-fold magnification (Anderson *et al.* 1996).

As for cervical sample-taking, for colposcopy a woman lies in the lithotomy position. After the examination of the vulva, the cervix is visualised with speculum. The nature of any discharge is

noted. The illuminated cervix is cleansed from excess discharge and mucus with a dry cotton wool swab or a swab soaked with normal saline. Thereafter, the cervix is examined with a colposcope starting with low magnification. In the colposcopic examination the squamous epithelium, the transformation zone, the squamocolumnar junction and the visible part of the columnar epithelium are checked for abnormalities (Coppleson *et al.* 1978).

During the examination, a 3% or 5% acetic acid solution is gently applied at the cervix. The application of the acetic acid solution causes tissue swelling and superficial coagulation of intracellular proteins, which is observed as reduced transparency of the cervical epithelium, a phenomenon also known as acetowhitening (Anderson *et al.* 1996). Acetowhitening is most prominent within areas with undifferentiated and dividing cells, e.g. in precancerous lesions, immature squamous metaplasia or healing or regenerative epithelium (International Agency for Research on Cancer 2005, Arbyn *et al.* 2008a), because of high nuclear density and consequent high protein concentration of these cells.

Colposcopic interpretation is based on the colposcopic examination and the acetowhitening pattern. The use of systematic methods, such as the Reid Colposcopic Index (RCI) (Table 3) (Reid and Scalzi 1985), in colposcopical grading is encouraged (Carriero *et al.* 1991), although the acetowhite sign is possibly the most important feature (Shaw *et al.* 2003). For histological confirmation, usually a punch biopsy is taken from the most suspicious area of the cervix. More than one biopsy may be taken in case of multiple suspicious focuses.

Based on a meta-analysis on the performance of diagnostic colposcopy by Mitchell *et al.*, colposcopic examination has an average sensitivity of 96% and specificity of 48% for any cervical abnormality (Mitchell *et al.* 1998). Respective estimates for detection of high-grade cervical lesions were 85% and 69%. In a more recent meta-analysis which is mostly based on the same original studies as the previous one, the sensitivity for any abnormality was between 87% to 99% while the specificity was 26% to 87%; sensitivity for the detection of high-grade lesions was 30% to 90% and specificity 67% to 97% (Olaniyan 2002).

Table 3 The Reid Colposcopic Index in colposcopy, modified from International Agency for Research on Cancer 2005 and Finnish Current Care Guidelines 2006

Scores	Colour	Margin and surface	Blood vessels	Iodine staining	Interpretation
0	• Transparent, pale white colour • Snow-white colour with intense surface shine • Acetowhitening beyond the margin of the transformation zone	• Flat lesion with feathery, indistinct of finely scalloped edges • Angular, jagged edges, geographical contour • Satellite lesions • Condylomatous or micropapillary contour	• Fine calibre, uniform • Fine punctuation or mosaic pattern	• Stains with iodine, mahogany-brown colour • Negative iodine staining appearing mustard-yellow colour if scores ≤ 3 thus far	
1	• Intermediate white colour, shiny, grey-white shade	• Regular-shaped, symmetrical lesion with sharp, straight edges	• Absent vessels	• Partial staining with iodine, variegated pattern	
2	• Oyster white, greyish, yellowish • Opaque	• Peeled edges • Internal demarcations within the lesion	• Coarse punctuation or mosaic pattern, randomly placed	• Negative iodine staining appearing mustard-yellow colour if scores ≥ 4 thus far	
Total	+	+	+	=	0-2: Normal, immature metaplasia, HPV atypia 3-4: CIN 1-2 5-6: CIN 2-3

Abbreviations: CIN 1-2, cervical intraepithelial neoplasia grades 1 and 2; CIN 2-3, cervical intraepithelial neoplasia grades 2 and 3

2.2.3. Other diagnostic tests

For example, in case the smear result is susceptive for glandular neoplasia in addition to colposcopy, other diagnostic tests may be necessary. Depending on the type of abnormal glandular cells, either endocervical or endometrial biopsy or curettage is usually performed.

2.2.4. Histologically confirmed lesions

If features suggestive of CIN or cancer (e.g. acetowhitening, punctuation, mosaic pattern, atypical vessels, sharp lines of demarcation, irregular surface and leukoplakia (Anderson *et al.* 1996)) are seen in colposcopic examination, the diagnosis is usually confirmed by a punch biopsy. The biopsy is then taken colposcopically using a special punch biopsy forceps, and no anaesthetics is needed. In some cases, the result of a colposcopic examination so strongly suggests a precancerous lesion requiring a local treatment that it is more appropriate to perform an immediate excision of the abnormal epithelium in local anaesthesia rather than take a punch biopsy. In this case, the histological confirmation is based on the examination of the whole excised cervical specimen.

A histopathologist makes the decision whether the epithelium in a cervical biopsy or excised specimen shows CIN and, if so, what the degree of it is. The histopathological features used as the basis of the diagnosis are: presence or absence of differentiation, maturation and stratification; proportion of the thickness of epithelium showing differentiation; presence of nuclear abnormalities such as increased nuclear cytoplasmic ratio, hypecromasia, nuclear pleomorphism and anisokaryosis; mitotic activity measured as number of mitotic figures, height in epithelium and presence of abnormal configurations (Anderson *et al.* 1996). Molecular pathological characteristics that are suggestive of progressive lesion are monoclonality, aneuploidy and loss of heterozygosity (LOH) (Fu and Berek 1988, Park *et al.* 1996, Chung *et al.* 2000). As for excised cervical specimens, the histopathological report should also indicate the size of the preparation, whether the transformation zone and all the lesion area are fully included, what the resection margins to the lesion are, and if there are any invasive components present (Finnish Current Care guidelines 2006). Histopathological features related to CIN 1, CIN 2 and CIN 3 are described in Table 4.

Table 4 Histopathological features of CIN 1, CIN 2 and CIN 3, based on Anderson *et al.* 1996

	Differentiation, maturation, stratification	Nuclear abnormalities	Mitotic activity
CIN 1	Good maturation	Present in minimal degree, mostly in the deeper layers of the epithelium	Some mitotic figures, no abnormal configurations
CIN 2	Maturation in the upper half of the epithelium	Present, extend higher in the epithelium	Mitotic figures present on the basal half of the epithelium
CIN 3	Differentiation and stratification may be completely absent or present only superficially	May extend throughout the thickness of the epithelium	Numerous, abnormal forms are frequent

Abbreviations: CIN 1, cervical intraepithelial neoplasia grade 1; CIN 2, cervical intraepithelial neoplasia grade 2; CIN 3, cervical intraepithelial neoplasia grade 3

Equal to cytological interpretations, histological interpretations are moderately well reproducible, with the exception of mild lesions (Stoler and Schiffman 2001).

Terminologies of histolopathological examination

The WHO terminology (Riotton *et al.* 1973) and the CIN terminology (Richart 1968, 1973) are both widely used for histopathological reporting. These terminologies are quite comparable, as mild dysplasia in the WHO terminology equals CIN 1 in the CIN terminology, moderate dysplasia equals CIN 2, and severe dysplasia and carcinoma *in situ* combined equal CIN 3 (Anderson *et al.* 1996, International Agency for Research on Cancer 2005).

The Bethesda System (Solomon *et al.* 2002), although primarily used for cytopathological reporting, has also been applied to histopathology to some extent. In this purpose LSIL category roughly equals mild dysplasia or CIN 1 (International Agency for Research on Cancer 2005), but it also includes a proportion of HPV related changes not included in other terminologies (Anderson *et al.* 1996). HSIL category equals the WHO terminology categories from moderate dysplasia to carcinoma *in situ* and the CIN terminology categories CIN 2 and CIN 3 (Anderson *et al.* 1996, International Agency for Research on Cancer 2005).

Management

Management of cervical lesions is primarily surgical, but it depends on the severity of the lesion and possibly on the age of the affected women. In Finland, the national recommendations given by the Finnish Medical Society Duodecim (Finnish Current Care guidelines 2006) should be followed.

Due to the primarily regressive nature of CIN 1 lesions in young women (under 30) (Östör 1993, Holowaty *et al.* 1999, Moscicki *et al.* 2004), they can be followed for spontaneous regression for up to 24 months instead of immediate treatment (Finnish Current Care guidelines 2006). Respective lesions in women of screening age (30 years or older) regress less often and are thus recommended to be treated with local excision of the lesion. CIN 2 and CIN 3 lesions are virtually always treated. Usually the treatment is local, but a hysterectomy may rarely be considered more beneficial – e.g. if the patient has some other co-existing gynaecological condition.

Local treatment may be excisional or destructive (Table 5). Excisional treatment methods are superior to destructive methods, as they result in a cervical specimen that can be histopathologically examined and evaluated for adequate removal of the targeted lesion. Although the excisional treatment methods are comparable in effectiveness, loop electrical excision procedure (LEEP; also called a large loop excision of the transformation zone i.e. LLETZ) is the most recommendable method for CIN treatment due to minimal morbidity related to this treatment and due to the representativeness of the resulting histological sample (Martin-Hirsch *et al.* 1999). Complications of local cervical treatment include perioperative pain and bleeding, prolonged postoperative bleeding, postoperative leucorrhoea and cervical stenosis (Larsson *et al.* 1982, Townsend and Richart 1983, Bostofte *et al.* 1986, Berget *et al.* 1987, Partington *et al.* 1989, Gunasekera *et al.* 1990, Kristensen *et al.* 1990, Oyesanya *et al.* 1993a, Oyesanya *et al.* 1993b, Alvarez *et al.* 1994, Santos *et al.* 1996, Martin-Hirsch *et al.* 1999). Also, cervical treatment may subject the woman to preterm rupture of the membranes and preterm delivery during future pregnancies and the newborn is more likely to have low birthweight (Crane 2003, Sadler *et al.* 2004, Kyrgiou *et al.* 2006a, Jakobsson *et al.* 2007).

Table 5 Local treatment methods, based on Arbyn *et al.* 2008a

Excisional treatment methods	Destructive treatment methods
LEEP, loop electrical excision procedure (or LLETZ, large loop excision of the transformation zone)	Radical diathermy (or electrocoagulation)
Cold knife conisation	Laser vaporisation
Laser excision	Cryotherapy (or cryocauthery)
NETZ, needle excision of the transformation zone (or SWETZ, straight wire excision of the transformation zone)	Cold coagulation

The increased risk of cervical cancer among women treated for CIN persists for decades (Kolstad and Klem 1976, Soutter *et al.* 1997, Kalliala *et al.* 2005, Soutter *et al.* 2006). The risk of residuals is higher in case of an incomplete removal of the primary lesion (Lopes *et al.* 1993, Baldauf *et al.* 1998, Dobbs *et al.* 2000, Flannelly *et al.* 2001, Paraskevaidis *et al.* 2004). Thus, all treated patients need to be adequately followed up. The post-treatment follow-up is conducted with colposcopies and cytology (Flannelly *et al.* 1997, Baldauf *et al.* 1998, Dobbs *et al.* 2000). In Finland the recommended follow-up regimen for women with treated CIN 1 is colposcopy and cervical smear at six months from the treatment and annual smears for at least two years afterwards; for women with CIN 2 or CIN 3, the initial follow-up examination at six months is followed by a cervical smear at 12 months from the operation, and an annual smear since, for at least up to five years from the treatment (Finnish Current Care guidelines 2006). Also, HPV DNA testing has been suggested for post-treatment follow-up (Nobbenhuis *et al.* 2001b). It seems to detect possible recurrences more efficiently than cytology (Paraskevaidis *et al.* 2004, Zielinski *et al.* 2004).

Treatment of an invasive cervical cancer depends on the stage of the disease (Table 6). The primary treatment of a localised cervical cancer is generally either surgery or radiation, which can sometimes be combined or used together with chemotherapy (International Agency for Research on Cancer 2005, International Agency for Research on Cancer 2007). In case of an advanced disease, the standard treatment is conducted as a combination of radiation and chemotherapy (Keys *et al.* 1999, Morris *et al.* 1999, Rose *et al.* 1999, Whitney *et al.* 1999).

Table 6 FIGO staging for cervical cancers and average 5-year survival by stage, based on International Agency for Research on Cancer 2005 and 2007

Stage				5-year survival
I			Invasive carcinoma strictly confined to the cervix	> 80%
	IA		Invasive carcinoma identified only microscopically	
		IA1	Invasion of the stroma ≤ 3 mm in depth and ≤ 7 mm wide	>99%
		IA2	Invasion of the stroma 4-5 mm in depth and ≤ 7 mm wide	97-98%
	IB		Clinically identifiable carcinoma confined to the cervix or microscopical carcinoma greater than stage IA	
		IB1	≤ 4 cm in size	80-90%
		IB2	> 4 cm in size	65-75%
II			Carcinoma extending beyond the cervix but not to the pelvic wall, involves vagina but does not extend to the lower third	
	IIA		No obvious parametrial involvement	> 70%
	IIB		Obvious parametrial involvement	40-50%
III			Carcinoma extending to the pelvic wall, involves the lower third of vagina, carcinoma cases with hydronephrosis or non-functioning kidney	40-50%
	IIIA		Involvement of the lower third of vagina, no extension to the pelvic wall	
	IIIB		Extension to the pelvic wall or hydronephrosis or non-functioning kidney	
IV			Carcinoma extending beyond the true pelvis or clinically involving the mucosa of the bladder and/or rectum	< 10%
	IVA		Spread or growth into adjacent pelvic organs	
	IVB		Spread to distant organs	

FIGO, International Federation of Gynaecology and Obstetrics

2.3. Vaccination against HPV infection

Currently, two vaccines against human papillomavirus infection are commercially available: Cervarix (by GlaxoSmithKline) and Gardasil (by Merck and Co. Incorporation). Both vaccines are made from L1 virus-like particles (VLPs) i.e. empty protein shells resembling the real virus, for which they are non-infectious. Both vaccines are targeted against HPV types 16 and 18 that are estimated to cause altogether 70.7% of cervical cancers worldwide (Muñoz *et al.* 2004). In addition, Gardasil additionally targets two low-risk HPV types, HPV 6 and 11 that cause most of the genital warts.

Up to the date, both vaccines seem safe and highly immunogenic (Koutsky *et al.* 2002, Harper *et al.* 2004, Villa *et al.* 2005, Mao *et al.* 2006): after three vaccine doses, the measured antibody levels for targeted HPV types have been 10-104 times higher than the antibody levels following

from natural infections (Harper *et al.* 2006, Villa *et al.* 2006). The results from vaccine efficacy trials have shown high efficacy against HPV 16 and 18 -related CIN 2 and 3 and adenocarcinoma *in situ* (AIS) lesions among adolescents and young women naïve for these HPV types and received at least one dose (of the three recommended) of the vaccine: with Cervarix the efficacy was 90% (97.9% CI 53-99%) (Paavonen *et al.* 2007), with Gardasil it was 95% (95% CI 85-99%) (The Future II Study Group 2007b). However, in unselected population the efficacy of Gardasil against HPV 16 and 18 -related CIN 2, CIN 3 and AIS was 44% (95% CI 26-58%), and against all CIN 2, CIN 3 and AIS only 18% (95% CI 1-31%) (The Future II Study Group 2007b). The efficacy of these HPV vaccines on invasive cervical cancer is not yet known, neither is the length of possible protection (Arbyn and Dillner 2007, European Centre for Disease Prevention and Control 2008, Arbyn *et al.* 2008a), and therefore cervical cancer screening is still considered necessary for the entire female population.

2.4. Cervical cancer screening

In 1968, Wilson and Jungner published the classic principles for successful screening for a disease: 1) the disease in question has to be an important health problem, 2) there must be an acceptable treatment for the disease, 3) adequate resources for diagnosis and treatment must be available, 4) the disease has a latent detectable phase, 5) there is a test suitable for screening purposes, 6) the screening test is acceptable to the population, 7) the natural history of the disease is reasonably well understood, 8) there is an agreed policy for patient management, 9) screening costs must remain at an acceptable level, and 10) screening has to be continuous (Wilson and Jungner 1968). Following these principles, the primary aim of a cervical cancer screening programme is to decrease the mortality related to the cancer of the uterine cervix by an early detection of cancer at the preclinical phase; also the incidence of cervical cancer (and further related morbidity) can be decreased, as in addition to preclinical cancers a large number of precancerous lesions are detected and treated. The impact of cytological screening on cervical cancer incidence and mortality is due to reduction in the number of invasive squamous cell cancers; the incidence of invasive adenocarcinoma is not similarly affected by screening (Mitchell *et al.* 1995, Nieminen *et al.* 1995).

2.4.1. Organisation of screening

With organised population-based screening with conventional cytology, more than 80% of cervical cancers and cervical cancer deaths can be prevented (Fidler *et al.* 1968, Hakama and Räsänen-Virtanen 1976, Hristova and Hakama 1997, Nieminen *et al.* 1999, Peto *et al.* 2004, International Agency for Research on Cancer 2005, Arbyn *et al.* 2008a). Non-organised (also known as spontaneous or opportunistic) cytological screening generally prevents cervical cancer to a much smaller extent (Sasieni *et al.* 1995, Hristova and Hakama 1997, Nieminen *et al.* 1999, Quinn *et al.* 1999, International Agency for Research on Cancer 2005). The difference in the screening effectiveness by the level of the organisation is likely to be related to the screening coverage: the population at highest risk is best reached with organised programmes (Stjernswärd *et al.* 1986, Baker and Middleton 2003).

An organised screening programme is built up as a chain of interventions, starting from defining the target population and the screening interval, and ending at registering the screening data in a central screening registry. The steps in between include inviting the target population for screening, organising the screening visits, collecting the screening tests, examining the screening tests and reporting the results to the participants, making the referrals for follow-up and further examinations when necessary, and organising proper management (Hakama *et al.* 1986, Hakama 1991, Anttila *et al.* 2008). The outcome of the screening programme is monitored and evaluated on the basis of the registered data. As to cervical cancer, in an optimally effective programme, screening is offered to at least all women between 35 and 64 years of age every three to five years, but not to women younger than 25 or older than 65 years (International Agency for Research on Cancer 2005). In low-resource settings, screening should be targeted to cover as much as possible of the population at risk, even if it implicates that screening can be offered once in a lifetime or with an extended interval (International Agency for Research on Cancer 2005).

Only in few countries in the world cervical cancer screening is performed population-based, organised and nationwide (Table 7) (International Agency for Research on Cancer 2005, Arbyn *et al.* 2008a, von Karsa *et al.* 2008).

Table 7 Policies for organised cervical cancer screening programmes in the world, modified from Anttila et al. 2004 and International Agency for Research on Cancer 2005

Country	Organised screening activity	Starting year	Target ages	Interval between normal tests	Smears per lifetime
Europe					
Austria	Regional (4% of the targeted population) in Voralberg	1970	20 or older	1	more than 50
Denmark	Nationwide	1996 (regional 1969)	23-59	3	13
Estonia	Regional pilot in Tartu, Tallin and Narva	2003	30-59[1]	5[1]	6
Finland	Nationwide	1970 (regional 1963)	30-60	5	7
France	Regional pilots in Bas-Rhin, Doubs, Isère and Martinique	1990-1994	25-65	3	14
Greece	Regional pilots in Ilia and Messinia Region and Ormylia	information not available	25-64	Ilia and Messinia 2, Ormylia 3 after 2 normals	14 or 20
Hungary	Nationwide	2003	25-65	3 after 2 normals	15
Iceland	Nationwide	1969 (regional 1964)	20-69	2 to 3	17 to 25
Ireland	Regional pilot in Mid Western Health Board Region	2000	25-60	5	8
Italy	Regional (52% of the targeted population) in 12 of 20 regions	most after 1996	25-64	3	14
Netherlands	Nationwide	1996 (regional 1970)	30-60	5	7
Norway	Nationwide	1995	25-69	3	15
Portugal	Regional in central Portugal	1990	20-64	3	15
Romania	Regional (3% of the targeted population) in Cluj county	2002	25-65	3	14
Slovenia	Nationwide	2003	20-64	3	15
Spain	Regional in Castilla y Leon	1986	25-65	3	14
Sweden	Nationwide	1973 (regional 1964)	23-60	3 for age 23-49, 5 for 50-60	12
United Kingdom	Nationwide	1995 (computerized call/recall 1988)	25-64	3 for age 25-49, 5 for age 50-64	12

Table 7 Continued

Country	Organised screening activity	Starting year	Target ages	Interval between normal tests	Smears per lifetime
Northern America					
Canada	Regional in Alberta, British Columbia, Manitoba, Nova Scotia, Ontario and Prince Edward Island	British Columbia 1960, Nova Scotia 1991, others 1999-2001	Ontario and Prince Edward Island 20-69, others 18-69	Alberta and Nova Scotia 1, others 2 after 3 normals	26, 27 or 51
Southern America					
Chile	Nationwide	1987	25-64	3	14
Colombia	Nationwide	1989	25-64	3	14
Cuba	Nationwide	1968	25-59	3	12
Africa					
South Africa	Regional (despite nationwide policy)	1997	30 or older	10	3[2]
Asia					
Japan	Nationwide	1982 (regional 1961)	30 or older	1 to 2[3]	more than 21
Republic of Korea	Nationwide	1999	30 or older	2	more than 21
Taiwan	Nationwide	1995	30 or older	3	more than 14
Australia and Oceania					
Australia	Nationwide	1991	18-69	2	27
New Zealand	Nationwide	1990-1991	20-69	3	17

[1] From von Karsa *et al.* 2008
[2] Recommendation in the national screening policy
[3] Reported by Sato *et al.* (Sato *et al.* 1997)

More often, a national recommendation or official policy for cervical cancer screening exists, but the delivery and quality of screening is inadequately monitored and evaluated. However, the term "organised screening" is used variably and the screening effectiveness may be low even in the presence of reported nationwide organised activity. Generally, the effectiveness of cervical cancer screening is compromised if any or several of the screening phases fail to succeed – e.g. invitational coverage or attendance remain low; sampling procedures or screening test performance do not meet the standards; diagnostic confirmations are, due to loss to follow-up, made only to a proportion of the screening test positives; or treatment is inefficient or not available due to limited health care resources.

2.4.2. Adverse effects

Despite the beneficial effects of population-based screening, it also causes adverse effects. Disadvantages of cervical cancer screening include anxiety caused by positive screening test or diagnosed lesion, repeated screenings due to borderline or mildly abnormal screening test results, unbeneficial colposcopies and other further examinations on women with no precancerous lesion, overtreatment of benign or non-progressive lesions, immediate treatment complications, long-term consequences of treatment on general and reproductive health, false reassurance related to false-negative screening test or colposcopy result, and opportunity costs to the health care system (Hakama 1991, Bell *et al.* 1995, Peters *et al.* 1999, Rogstad 2002, Ideström *et al.* 2003, International Agency for Research on Cancer 2005). In an organised assessment, the balance between screening-related health benefits and adverse effects is more acceptable than the absence of organisation, and the cost-effectiveness is better (International Agency for Research on Cancer 2005). The factors affecting the extent of adverse effects of cervical cancer screening include the age range of the targeted women, screening interval and quality of screening: starting to screen under the age of 25 years and continuing to the age of 65 years and over increases the adverse effects without very much increasing the effectiveness; screening with a one-year interval does not increase the effectiveness very much compared to 3- to 5-yearly screening; low specificity of the screening test leads to high numbers of false positives and low specificity of a diagnostic test leads to unnecessary treatments (van Ballegooijen *et al.* 2000, Anttila *et al.* 2004, Anttila *et al.* 2008).

2.4.3. Screening technologies

Based on the literature, four different technologies are considered suitable as primary tests for population-based cervical cancer screening (Noorani *et al.* 2003, International Agency for Research on Cancer 2005, Arbyn *et al.* 2008a). These technologies are conventional cytology, liquid-based cytology, automation-assisted cytology and HPV DNA testing. Also, a few other screening methods, including visual inspection with acetetic acid or Lugol's iodine, have been proposed and, to some extent, used or evaluated for screening.

Conventional cytology

Screening with conventional cytology has resulted in a marked decrease in cervical cancer incidence and mortality in a number of countries. However, in others the effect of screening has been virtually nonexistent (International Agency for Research on Cancer 2005). In addition to the lack of organisation, the blame has often been laid on the quality of conventional cytology. Worldwide, the variation in the accuracy of conventional cytology is large: estimates for the sensitivity for CIN 2+ vary from about 30% to 90% and, respectively, for the specificity from 85% to nearly 100% (Soost *et al.* 1991, Nanda *et al.* 2000, International Agency for Research on Cancer 2005, Arbyn *et al.* 2008c). Reproducibility of conventional cytology measured through intra- and interobserver variability has been at best moderate to good (Klinkhamer *et al.* 1988, Branca *et al.* 1996, Cocchi *et al.* 1997, Branca *et al.* 1998, Woodhouse *et al.* 1999, Cibas *et al.* 2001, Gupta *et al.* 2001, Chhieng *et al.* 2002).

In 2004, Nieminen *et al.* estimated that in Finland the cross-sectional sensitivity of conventional cytology equal to ASC-US or worse (ASC-US+) to detect CIN 2 and more severe lesions (CIN 2+) was 93% (95% CI 82-99%) and the sensitivity to detect CIN 3 or invasive cancer was 95% (95% CI 77-100%) (Nieminen *et al.* 2004). With respective cutoffs for cytology and histology, cross-sectional specificities were 77% (95% CI 75-79%) and 76% (95% CI 75%-78%). Similarly, sensitivities of conventional LSIL+ cytology for CIN 2+ and CIN 3+ were 83% (95% CI 69-92) and 86% (95% CI 65-97%), and specificities 94% (95% CI 93-95%) and 93% (95% CI 92-94%), respectively. These

esimates may, however, be slightly biased as colposcopies and histological verification were only provided on the basis of abnormal cytology equal to LSIL+.

Liquid-based cytology

Liquid-based cytology (LBC) is a modification of conventional cytology that is widely used for primary cervical cancer screening. With this technology cervical samples are collected into liquid solution, which is then used for cytological slide preparation. The residual material may be used for additional testing, e.g. HPV DNA detection. Several LBC tests are commercially available, among which ThinPrep (by Cytyc Corporation) and the BD SurePath System (formerly AutoCyte PREP System, by BD Diagnostics, Diagnostic Systems – TriPath) are the best-known and most studied (Arbyn *et al.* 2008a).

Recent randomised studies and meta-analyses have shown that the performance of LBC in terms of CIN 2+ detection is comparable to conventional cytology (Davey *et al.* 2006, Ronco *et al.* 2007b, Arbyn *et al.* 2008b). However, some studies have reported a lower number of unsatisfactory smears with LBC than with conventional cytology, and the time needed for interpretation is possibly shorter with LBC (PRISMATC Project Management Team 1999, Colgan *et al.* 2004, Dowie *et al.* 2006, Doyle *et al.* 2006, Ronco *et al.* 2007b).

Based on an Italian cost-effectiveness analysis, LBC is equivalent to conventional cytology only if the cost of a test unit is lower than that of a conventional smear and if colposcopies are reasonably inexpensive, or if the number of inadequate smears is particularly high (Giorgi-Rossi *et al.* 2007). In the recently published European guidelines for quality assurance in cervical cancer screening, more studies on costs, effects and cost-effectiveness of LBC are warranted (Arbyn *et al.* 2008a).

Automation-assisted cytology

Automation-assisted cytology is another modification of the conventional cytology, in which the cytological smear is at least partially examined by a computerised system. The first generation of

automation-assisted systems (Papnet by former Neuromedical Systems Incorporation, AutoPap by NeoPath Incorporation) was designed to analyse conventional smears, but more recently automation-assistance has been incorporated to LBC systems, too (Arbyn *et al.* 2008a).

In a number of studies, automation-assisted cytology has performed at least comparable to conventional cytology (Kok and Boon 1996, Michelow *et al.* 1997, PRISMATC Project Management Team 1999, Doornewaard *et al.* 1999a, Doornewaard *et al.* 1999b, Duggan 2000, Kok *et al.* 2000, Nieminen *et al.* 2003, Irwig *et al.* 2004). Automation-assistance has been suggested especially suitable for rapid rescreening of manually screened smears as means of quality control (Wilbur *et al.* 1996, Koss *et al.* 1997, Halford *et al.* 1999, Bergeron *et al.* 2000). One large prospective study reported that automation-assistance yields three-fold productivity in comparison to manual cytological examination (PRISMATC Project Management Team 1999).

Studies on the performance of automation-assisted LBC methods (e.g. ThinPrep Imaging System by Hologic Company, and BD FocalPoint Slide Profiler by BD Diagnostics) are yet relatively few and preliminary. So far automation-assisted LBC has been reported to result in equal or increased detection of high-grade lesions compared to conventional cytology or manually analysed LBC (Cengel *et al.* 2003, Biscotti *et al.* 2005, Bolger *et al.* 2006, Dziura *et al.* 2006, Chivukula *et al.* 2007, Miller *et al.* 2007, Roberts *et al.* 2007, Papillo *et al.* 2008) and to markedly reduced screening time (Biscotti *et al.* 2005, Bolger *et al.* 2006, Roberts *et al.* 2007, Schledermann *et al.* 2007). Automation-assisted LBC method with a ranking system is suggested to be safe and useful (Parker *et al.* 2004, Passamonti *et al.* 2007).

HPV DNA testing

Genomes of oncogenic HPVs and their transcripts can be detected by using numerous PCR-based methods and hybridization techniques (International Agency for Research on Cancer 2007), several of which have been suggested for primary screening (Cuzick *et al.* 1999, Brink *et al.* 2007, Wahlström *et al.* 2007, Castle *et al.* 2008a, Castle *et al.* 2008b). However, most of the knowledge on HPV DNA testing in primary screening has been acquired by three clinically validated test methods: commercial Hybrid Capture 2 assay (also HC 2, by Qiagen Corporation), polymerase chain reaction (PCR) with consensus primer pair GP5+/6+ (an extended version of GP5/6) and PCR

with degenerate primers MY09/11 (or modification PGMY09/11) (de Roda Husman *et al.* 1995, Jacobs *et al.* 1995, Gravitt *et al.* 1998, Cuzick *et al.* 1999, Gravitt *et al.* 2000, Arbyn *et al.* 2006).

HC 2 is a Food and Drug Administration (FDA) approved commercial product that detects HPV DNA by hybridization with cocktails of synthetic RNA probes complimentary to genomic sequences of 13 high-risk HPV genotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68, in probe cocktail B) and 5 low-risk genotypes (HPV 6, 11, 42, 43 and 44). PCR with GP5+/6+ and PCR with MY09/11 detect mucosal high-risk HPV types by amplification of highly conserved L1 region and, contrary to HC 2, they allow direct HPV genotyping by the detection of the PCR-amplified products. All these validated tests have high analytical sensitivity and specificity (Hesselink *et al.* 2006, Brink *et al.* 2007) and the intra- and inter-laboratory agreement rates between these methods range from good to excellent, i.e. they are well reproducible (Schiffman *et al.* 1995, Qu *et al.* 1997, Peyton *et al.* 1998, Jacobs *et al.* 1999, Gravitt *et al.* 2000, Castle *et al.* 2002a, Castle *et al.* 2004, Kulmala *et al.* 2004, Carozzi *et al.* 2005). Compared to GP5+/6+ PCR, PCR with MY09/11 seems to have a slightly distinctive test sensitivity for targeted HPV types (Qu *et al.* 1997). HC 2 has been described to cross-react with some low-risk HPV types (Peyton *et al.* 1998, Poljak *et al.* 2002, Castle *et al.* 2008c).

Various studies reporting cross-sectional performance of high-risk HPV DNA testing in comparison to cytology have been published. Summarised in a few meta-analysis and review articles, HPV DNA testing has proved to have cross-sectional sensitivity but lower specificity for CIN 2+ than cytology (Cuzick *et al.* 1999, Arbyn *et al.* 2006, Cuzick *et al.* 2006, Davies *et al.* 2006, Koliopoulos *et al.* 2007). Randomised studies on HPV DNA testing in population-based screening are conducted, in Finland, Canada (the Canadian Cervical Cancer Screening Trial i.e. CCCaST), India, Italy (the New Technologies for Cervical Cancer Screening i.e. NTCC trial), the Netherlands (the Population-Based Screening Study Amsterdam i.e. POBASCAM trial), Sweden (the Swedescreen trial) and the United Kingdom (the ARTISTIC trial). An overview of the randomised study protocols and published results is shown in Table 8.

Table 8 Randomised studies on HPV DNA testing in population-based screening: designs and published results

Trial and design	Comparison	Subjects	Age range	Published results	Other	References
Canada (CCCaST)						
RCT	HC 2 vs. conventional cytology (HC 2 and cytology vs. cytology and HC 2)	10,154	30-69	Cross-sectional Se for CIN 2+: HC 2 94.6%, ASC-US+ cytology 55.4% vs. LSIL+ cytology 42.2%. Cross-sectional Sp using CIN 2+: HC 2 94.1%, ASC-US+ cytology 96.8%, LSIL+ cytology 99.1%.	At rlu ratio cutoff 2.00 for HC 2 Se for CIN 2+ was 81.1% and Sp 95.5%.	(Mayrand *et al.* 2006, Mayrand *et al.* 2007)
India						
Cluster RCT (by primary health centers)	HC 2 vs. VIA, cytology or control	142,701	30-59	No difference in cross-sectional detection of cancer or CIN in comparison to cytology.	HPV DNA test objective and reproducible, but requires high investments.	(Sankaranarayanan *et al.* 2005)
Italy (NTCC)						
RCT, Phase 1	HC 2 and LBC vs. conventional cytology	45,307	25-60	Among women aged 35-60, cross-sectional relative Se of HC 2 for CIN 2+ was 1.43 and relative PPV 0.58, compared to ASC-US+ cytology. Among women aged 25-34, using cytology triage, relative Se of HC 2 for CIN 2+ was 1.58 and relative PPV 0.78.	Among women aged 35-60, with rlu ratio cutoff 2.00 relative Se of HC 2 for CIN 2+ was 1.41 and relative PPV 0.75, compared to ASC-US+ cytology. Among women aged 25-34, using cytology triage, relative Se of HC 2 with rlu ratio cutoff 2.00 for CIN 2+ was 1.55 and relative PPV 1.02.	(Ronco *et al.* 2006a, Ronco *et al.* 2006c, Ronco *et al.* 2007a)
RCT, Phase 2	HC 2 vs. conventional cytology	49,481	25-60	Compared to ASC-US+ cytology, relative cross-sectional Se of HC 2 for CIN 3+ was 2.06 and relative PPV 0.86. Among women aged 25-34 respective estimates were 2.61 and 0.66.	Compared to ASC-US+ cytology, with rlu ratio cutoff 2.00 relative Se of HC 2 for CIN 3+ was 2.06 and relative PPV 1.22. Among women aged 25-34 respective estimates were 2.61 and 0.75.	(Ronco *et al.* 2008)

Table 8 Continued

Trial and design	Comparison	Subjects	Age range	Published results	Other	References
Netherlands (POBASCAM)						
RCT	GP5+/6+ vs. conventional cytology	17,155 (44,102 whole RCT)	29-56 (29-61 whole RCT)	Over two screening rounds, during follow-up of median 7.2 years and equal proportion (1.1%) of women were diagnosed with CIN 3+ with GP5+/6+ and BMD+ cytology. With GP5+/6+ more of these lesions were detected during the baseline round (0.8%) than during the subsequent round (0.3%), in comparison to cytology (0.5% and 0.6%, respectively).	5-year cumulative risk of CIN 3+ in women with negative HPV DNA test and normal cytology was 0.1%, whereas risk of women with negative HPV DNA test only was 0.2% and risk of women with normal cytology only was 0.6%.	(Bulkmans *et al.* 2004, Bulkmans *et al.* 2007b)
Sweden (Swedescreen)						
RCT	GP5+/6+ and conventional cytology vs. conventional cytology	12,527	32-38	During follow-up of mean 4.1 years 8% more CIN 2+ findings were observed by GP/6+ and cytology than by cytology only. With GP5+/6+ and cytology CIN 2+ lesions were detected in 51% higher rate during prevalence screening in comparison to cytology only, and in 42% lower rate during incidence screening.	Increase in CIN 2+ detection with GP5+/6+ and cytology was highest among CIN 2 lesions: during prevalence screening increase in comparison to cytology was 101% and reduction during incidence screening was 15%.	(Naucler *et al.* 2007)
United Kingdom (ARTISTIC)						
RCT	HC 2 vs. LBC (HC 2 and LBC vs. cytology and LBC)	24,510	20-64	No cross-sectional comparison by randomisation reported.	Prevalence peak of high-risk HPV infections among women aged 20-24, of which 40% infected.	(Kitchener *et al.* 2006)

Abbreviations: BMD+, borderline or mild dysplasia or worse; RCT, randomised controlled trial; HC 2, Hybrid Capture 2, GP5+/6+, polymerase chain reaction with general primer pair GP5+/6+; LBC, liquid-based cytology; Se, sensitivity; Sp, specificity; CIN 2+, cervical intraepithelial neoplasia grade 2 or more severe lesion; CIN 3+, cervical intraepithelial neoplasia grade 3 or more severe lesion; rlu ratio; ratio of relative light units; PPV, positive predictive value

From the Canadian, Indian and Italian randomised HPV screening trials, only cross-sectional results are currently available. The Canadian and Italian trials have confirmed the higher detection of high-grade lesions with HPV DNA testing than with conventional cytology (Mayrand *et al.* 2006, Ronco *et al.* 2006a, Ronco *et al.* 2006c, Mayrand *et al.* 2007, Ronco *et al.* 2007a, Ronco *et al.* 2008), whereas the Indian trial resulted in equal detection rates between the screening methods studied (Sankaranarayanan *et al.* 2005). The studies from the Netherlands and Sweden have already reported results over two screening rounds. Both of these have suggested an earlier detection of high-grade lesions with HPV DNA testing in comparison to conventional cytology (Bulkmans *et al.* 2007b, Naucler *et al.* 2007). Of the trial from the United Kingdom (Kitchener *et al.* 2006) no cross-sectional results by random allocation (intention to screen) have been published yet.

For population-based screening with the HC 2 assay alone, a slightly increased test positivity cutoff (rlu ratio 2.00 or 3.00) has been suggested to optimise the balance between sensitivity and specificity (Hesselink *et al.* 2006, Ronco *et al.* 2006a, Ronco *et al.* 2006c). However, in one screening study the optimal balance was observed at a much higher cutoff (rlu ratio 15.6) (Kulmala *et al.* 2004). A few studies have reported that by using the rlu ratio cutoff 10.00 the sensitivity and specificity estimates of HC 2 for high-grade lesions become close to those of cytology (Kuhn *et al.* 2000, Schiffman *et al.* 2000, Clavel *et al.* 2001).

The relation of the viral load to the severity of underlying lesion has also been studied on a more general level (Josefsson *et al.* 2000, Ylitalo *et al.* 2000, van Duin *et al.* 2002, Gravitt *et al.* 2003, Prétet *et al.* 2004, Gravitt *et al.* 2007). Based on the literature, the risk of high-grade precancerous lesion and cervical cancer seems to grow with an increasing viral load. However, the viral load is not necessarily high in case of CIN 3 or cervical cancer (Lorincz *et al.* 2002, Snijders *et al.* 2003), and if it is, the severe lesion is likely to be surrounded by a co-existing lesion of CIN 1 or CIN 2 (Sherman *et al.* 2003b).

A negative HPV DNA test result in conjunction with a normal cytology has been associated with a very low risk of 0.16% for CIN 3 or cancer during a 45-month follow-up in comparison to 4.54% incidence of CIN 3+ among women with either positive HPV test or abnormal cytology or both (Sherman *et al.* 2003a). Very similar results have also been reported on the basis of pooled data

from seven European screening studies: during a follow-up of six years (72 months), the cumulative incidence of CIN 3 or cancer was 0.27% among women negative to HPV DNA, whereas the respective cumulative incidence among women with negative cytological test was significantly higher, 0.97%; and of women positive to HPV DNA but with negative cytology result 10% developed CIN 3 lesion or worse during the six-year follow-up compared to the 2.7% of the HPV DNA negative but cytology positive women (Dillner *et al.* 2008a).

In women with normal cytology, the absolute risk of subsequent CIN 3+ during the follow-up is especially high (9.3% in five years) among older (40 to 50 years old) women with a positive HPV DNA test, and especially low (0.4% in five years) among older women negative to high-risk HPV DNA; the respective risk estimates among younger (22 to 32 years old) women are intermediate (5.5% for HPV DNA positives and 0.8% for HPV DNA negatives in five years) (Kjaer *et al.* 2006).

The cost-effectiveness of primary screening with an HPV DNA testing has been tentatively studied to some extent. In the United States, where cervical cancer screening has traditionally been one-yearly, it has been estimated that HPV screening in conjunction with cytology or cytological screening with reflex HPV DNA test every 2 to 3 years would have higher cost-effectiveness than the annual cytological screening (Goldie *et al.* 2004). Based on a study using the Swedscreen trial data HPV DNA testing in combination with cytology can be cost-effective only if the screening interval is extended up to 9 years, if compared to the screening with conventional cytology only (Bistoletti *et al.* 2008). The Italian study suggested that HPV DNA testing with cytology triage or wiht test positivity cutoff higher than the standard one, may reduce the need for resources per each CIN 2+ lesion detected in comparison to conventional cytology, but the unit cost of an HPV DNA test should be at maximum 30% higher than of a conventional smear (Giorgi-Rossi *et al.* 2007). In low-income countries, the HPV screening has been reported unaffordably expensive (Legood *et al.* 2005).

In addition to primary screening, HPV DNA testing has been suggested for triaging of ASC-US cytology (Arbyn *et al.* 2004, Arbyn *et al.* 2005) and LSIL cytology for women of 35 years or older (Ronco *et al.* 2007c) but not for all women, and for post-treatment follow-up of CIN lesions (Nobbenhuis *et al.* 2001b).

Other technologies

In some European and Latin American countries colposcopy is used as the primary screening test, but there is only limited information available on the performance of screening colposcopy (International Agency for Research on Cancer 2005). Only a few studies have reported sensitivity and specificity of screening colposcopy for the detection of CIN 2+ lesions, and between these studies there is notable variation in sensitivity and specificity: estimates for sensitivity vary from 13.2% to 90.7% and for specificity from 77.0% to 99.2% (Davison and Marty 1994, Hilgarth and Menton 1996, Schneider *et al.* 2000, Belinson *et al.* 2001). As colposcopy is generally expensive, time-consuming and requires extensively trained personnel to be properly conducted, it is not recommended for primary screening (Kyrgiou *et al.* 2006b).

Two techniques based on direct visual inspection (DVI) of the cervix, i.e. visual inspection with application of acetetic acid (VIA) or Lugol's iodine solution (VILI), have been studied in low-resource settings. In both VIA and VILI, the woman lies in the lithotomy position and the cervix is studied with a naked eye before and after the application of either 3-5% acetetic acid (VIA) or Lugol´s iodine solution (VILI). The result is available on-site, based on the acetowhite (VIA) or iodine uptake (VILI) pattern, and the need for treatment can be immediately determined. In the published studies on DVI techniques, VIA was shown to be equally or more sensitive but substantially less specific than cytology to detect high-grade lesions; VILI was more sensitive but equally specific as VIA (Sankaranarayanan *et al.* 2004a, Sankaranarayanan *et al.* 2004d, International Agency for Research on Cancer 2005, Arbyn *et al.* 2008c). Compared to e.g. cytology or HPV DNA testing, visual inspection methods are simple and inexpensive. Moreover, primary health care workers can be relatively easily trained for the test performance, and the test result is immediately available, which enables a direct treatment without extensive loss to follow-up (Sankaranarayanan *et al.* 1998, Sankaranarayanan *et al.* 1999, Denny *et al.* 2002, Sankaranarayanan *et al.* 2004c).

Other possible technologies, e.g. molecular progression or predictive markers such as antibodies to cyclin dependent kinase inhibitor $p16^{INK4a}$ (Klaes *et al.* 2001, Klaes *et al.* 2002) or detection methods for HPV E6/E7 messenger RNA (Lie and Kristensen 2008) have not been adequately studied as primary methods for population-based screening (International Agency for Research on

Cancer 2005, International Agency for Research on Cancer 2007, Wentzensen and von Knebel Doeberitz 2007).

2.4.4. Evaluation for effect

The effect of screening refers either to efficacy or effectiveness of the conducted screening practice: efficacy is the effect of screening on the studied outcome under ideal conditions (in optimal research setting), whereas effectiveness is the effect of routine screening on the outcome in the target population. As the ultimate aim of a cervical cancer screening programme is to decrease mortality from the disease, the effect of routine screening is primarily indicated by observed cervical cancer mortality in the target population in the presence of screening compared to observed or expected mortality in the absence of screening (Anttila *et al.* 2008). In case of cervical cancer screening, another valid indicator of the effectiveness of an organised screening programme is the incidence of invasive disease in the target population, especially the incidence of invasive cervical cancers diagnosed after a screening visit (subsequent cancers) or between the screening rounds (interval cancers).

The evaluation of the effectiveness of routine cervical cancer screening is essentially dependent on the existence of cancer and screening registries. It can be conducted by applying the study designs on interventions (randomised, cohort and case-control designs). Most unbiased estimates are achieved within a randomised setting, by comparing the outcomes between the intervention group (e.g. women invited to cervical cancer screening or women screened applying a novel screening technology) and the control group (e.g. women not invited to cervical cancer screening or women screened with the standard screening technology). In Finland, a cluster randomised design was used for the first time for the evaluation of a routine screening practice was when the mammography screening programme was launched in the late 1980s (Hakama *et al.* 1997). A randomised design has later been applied at an individual level in the evaluation of automation-assisted vs. conventional cytology in cervical cancer screening (Nieminen *et al.* 2003) and when the programme for colorectal cancer screening with foecal occult blood test was introduced (Malila *et al.* 2008).

However, most of the evaluation studies on cervical cancer screening have not been conducted randomised. A lot of the information on the screening effectiveness is based on cohort studies (Fidler *et al.* 1968, Hakama and Räsänen-Virtanen 1976, Miller *et al.* 1976, Lynge *et al.* 1989) and time trend analyses (Hakama 1982, Läärä *et al.* 1987, Anttila *et al.* 1999). Compared to randomised studies, the results of which are quite straight-forward, these non-randomised studies need to be interpreted more cautiously.

In general, since the development of cervical cancer from the initial high-risk HPV infection is a slow and rare process, follow-up studies on cervical cancer, irrespective of the intervention study design, usually need to be large and very long-term to reach adequate statistical power.

Sometimes the evaluation of screening outcome with the invasive cervical cancer as the endpoint is considered inappropriate or not applicable, e.g. due to ethical issues or the rarity of this condition among the population studied (International Agency for Research on Cancer 2007). Hence, cervical cancer screening programmes have also been evaluated cross-sectionally, using various intermediate parameters for performance, such as rates of coverage, attendance, test positivity or precancer detection, to predict the long-term screening effectiveness. Using any precancerous state as a surrogate for invasive cervical cancer is always imperfect, since only a proportion of all precancerous lesions would ever progress to invasion, and we do not know which of them will. Of the cervical precancerous lesions, CIN 3 is the most reliable surrogate endpoint, as for CIN 2 and especially for CIN 1 lesions the risk of progression to invasion is low (Östör 1993, Holowaty *et al.* 1999, Moscicki *et al.* 2004) and the inter- or intraobserver variation is large (Stoler and Schiffman 2001).

The use of cross-sectional process parameters for the evaluation of cervical cancer screening programmes has its limitations due to several methodological issues as well (Hakama 1991). First, precancerous cervical lesions and invasive cancers detected with screening are likely to be slowly developing and, thus, they are relatively benign in nature considering the outcome of screening (length bias). Second, screen-detected lesions are basically detected and treated at preclinical phase, i.e. prior to which they would have been detected in the absence of screening, but that does not necessarily mean the diagnosis and the potential treatment are beneficial e.g. in terms of increasing the life expectancy or improving the quality of life (lead time bias). Futher, the

estimated validity of a screening test is easily biased if test positives and negatives are verified with the gold standard (generally colposcopy and biopsies) in different fractions (verification bias) or the gold standard is inaccurate or poorly reproducible. Therefore, even ineffective screening programmes may result in some beneficial changes in process parameters (Anttila *et al.* 2008). Process parameters have also been shown to vary between geographical areas (Anttila *et al.* 2004, NHS Health and Social Care Information Centre 2005, Ronco *et al.* 2006b), at least partly due to differences in the background risks of cervical cancer (Anttila *et al.* 2004).

The most important benefits of a cervical cancer screening programme are, obviously, cancer deaths and invasive cervical cancers avoided. Other beneficial effects of cervical cancer screening include psychological reassurance after a negative screening test or successful local treatment of a precancerous cervical lesion, preserved fertility due to the fact that precancers are locally treated, and social benefits and health care cost savings due to decreased cervical cancer mortality and morbidity (Hristova and Hakama 1997). However, as screening is not only beneficial, the evaluation of a screening programme should also consider the unwanted effects of screening, weighed against the advantages of screening (Anttila *et al.* 2008). These disadvantages of cervical cancer screening are anxiety related to positive screening test result or diagnosed lesion, repeated screenings due to equivocal screening test results, unnecessary colposcopies, overtreatment of non-progressive cervical lesions, treatment complications and consequences, false psychological reassurance related to false-negative results, and health care costs (Hakama 1991, Bell *et al.* 1995, Peters *et al.* 1999, Rogstad 2002, Ideström *et al.* 2003, International Agency for Research on Cancer 2005).

3. Aims of the study

The study was conducted within the framework of health services research that applies a randomised design: the data was routinely derived from the Finnish organised cervical cancer screening programme. The aim of the study was to evaluate the applicability and cross-sectional performance and validity of two new screening technologies, automation-assisted cytology and primary HPV DNA testing, in comparison to conventional cytology during the implementation phase of the new screening technologies.

The more detailed aims of the original publications were:

1. to assess the cross-sectional performance and validity of automation-assisted screening in comparison to conventional screening (I, II),
2. to assess the cross-sectional performance and validity of screening with a primary HPV DNA test in comparison to conventional screening (III, IV),
3. to relate the semiquantitative information on the HPV viral load to the CIN detection (V) and
4. to relate the cross-sectional information on screening performance to the screening effectiveness (VI).

For cross-sectional performance and validity, the parameters of interest were test positivity rate, histological detection rate, relative sensitivity, relative specificity and positive predictive value (PPV). Relative sensitivity, relative specificity and PPV were estimated by using several cutoffs for test positivity and histological detection. Also, the variation in performance by the screening laboratory was studied.

4. Materials and methods

4.1. The population-based cervical cancer screening programme in Finland

The Finnish organised programme for cervical cancer screening was originally implemented in 1963 as a regional pilot. Since 1968 it has been running nationwide. The programme is targeted for the women aged 30 to 60 years, roughly 1.2 million in number (Anttila and Nieminen 2000, Finnish Cancer Registry 2007). The screening interval after a normal test result is five years. In case intensified (or risk group) screening is indicated due to abnormal screening test result or reported symptoms (Hakama *et al.* 1979, Viikki *et al.* 1998, 2000a, Viikki *et al.* 2000b, Rosenthal *et al.* 2001), the screening interval is shortened to one year (Anttila and Nieminen 2000). The national Population Registry is used to identify the women in the target population, for which the invitational coverage is very high, ranging from 92.8% among the 30-year-olds to approximately 99% among women aged 40 to 55 (Finnish Cancer Registry 2007). Invitations are sent as personal letters. Every year approximately 250,000 women get an invitation letter and 180,000 women attend. The average attendance rate in the programme is 71%. Screening is free of charge for those who attend.

As to the Primary Health Care Act (since 1972) and Decree on Primary Health Care (since 1992) the individual municipalities are responsible for making practical screening arrangements and the screening-related costs in Finland (www.finlex.fi, FINLEX Data Bank 2008). Thus, the targeted ages (range from 20 to 65 years) and the screening details (use of invitations and reminders, use of pre-fixed appointment times, places for sample-taking, risk group screening arrangements, etc.) are determined by municipal-level authorities. Screening visits are most often organised in the outpatient clinics of regional health centers and the screening samples are collected by specifically trained registered nurses and midwifes. In 2008, there were 415 municipalities in Finland with a population ranging from 116 up to nearly 570,000 inhabitants (www.kunnat.net, Local and Regional Government Finland 2008). Altogether 14 laboratories were involved in analysing the samples from the organised cervical cancer screening programme.

4.1.1. Conventional screening protocol

During the screening visit a trained nurse or midwife does the cervical sampling, prepares and fixes the VCE smear and fills in an information form with each participant's recent gynaecological history. Completed forms and fixed smears are sent to the appointed screening laboratory for further processing and interpretation. Primary smear interpretation is performed by a cytotechnician. A pathologist re-screens all the slides with any abnormalities and possibly a small fraction of the slides classified as normal. The screening laboratory reports the screening test results to the women attended in a personal letter. If colposcopy or other further examinations are indicated on the basis of the screening result, the woman is often first contacted by phone.

Until the end of 2005, most screening laboratories used the Papanicolaou classification for cytopathological examination, but they have since changed into classification with The Bethesda System (TBS) year 2001 version (Solomon *et al.* 2002). Women with Pap class III-V smears (corresponding to ASC-H, LSIL, HSIL and AGC-FN in TBS 2001) are directly referred for colposcopy. Pap class II smears (corresponding to ASC-US, AGC-NOS and reactive changes in TBS 2001) are generally recommended for a control smear after 6 to 12 months or after a possible medicinal treatment; however, a repeated Pap class II smear is generally considered as an indication for colposcopy. In most municipalities, the women with Pap class II smear who reported bleeding symptoms or no histologically confirmed lesion in colposcopy due to Pap class III-V smear are invited to intensified screening the following year.

Screening-induced colposcopies and other possible confirmatory tests are mainly performed in regional hospitals, where also the histologically confirmed lesions are treated and the post-operational follow-up is conducted. Histological classification is based on the WHO terminology.

4.1.2. Data registration

Information on all organised cancer screening programmes in Finland is collected from the screening centres and laboratories into the databases of the National Research and Development Centre for Welfare and Health (STAKES) that are maintained at the Mass Screening Registry

department of the Finnish Cancer Registry. The data registration activity is based on the Act and the Decree on the National Personal Records Kept under the Health Care System, effective since 1989 (www.finlex.fi, FINLEX Data Bank 2008). The registered data on organised cervical cancer screening includes invitational information (year, municipality, reason for invitation) originally drawn from the national Population Registry, information on screening visits and results (time of screening visit, municipality, self-reported gynaecological anamnesis, screening test result, recommendations for management) derived from screening laboratories, and information on eventual further examinations and their results (time of referral, time of examinations, diagnoses, primary treatment) reported by screening laboratories and pathology laboratories of regional hospitals. The data is registered at an individual level using the unique personal identifier given to all permanent residents in Finland as the primary key for linkages.

The database on organised cervical cancer screening does not collect any information on smears from outside the organised programme. In addition, up to the end of this study it did not separate cervical lesions by histology, i.e. adenomatous and squamous lesions were recorded as the same.

4.2. Randomised implementation of new technologies

An experimental screening strategy with automation-assisted cytology and HPV DNA testing has been applied into service screening in Finland in a randomised setting (Nieminen *et al.* 2003, Nieminen *et al.* 2004, Anttila *et al.* 2006). In this experiment regarding new screening technologies, the women invited to routine five-yearly screening are individually randomised to be screened with automation-assisted cytology, primary HPV DNA test or conventional cytology, which is the principal reference.

Before the new screening technologies were incorporated to the service screening, the proposed screening protocols were approved by the responsible authority in Finland, the National Authority for Medicolegal Affairs (TEO). Also, the new screening protocols were judged ethically acceptable by the ethical committee of the National Research and Development Centre for Welfare and Health (STAKES) under the Ministry of Social Affairs and Health (automation-assisted cytology) and the Ethical Committee of Obstetrics and Gynaecology in Hospital District of Helsinki and Uusimaa (HPV screening). The permission of the National Authority for Medicolegal Affairs stated, on the

basis of the Act of the Medical Use of Human Organs and Tissues (2001), that collecting an informed consent from each attendant was not required, as the randomised implementation of new screening technologies was expected to result in a very large number of screening tests and because screening, also with new screening technologies, was regarded as a routine practice, not as a clinical trial.

Automation-assisted cytology using the Papnet system (by former NSI Inc.) was first implemented into service screening, in the year 1999. During 1999-2002, one third of the screening samples in six well-established screening laboratories (laboratories of the Finnish Cancer Organisations (FCO) in Helsinki, Kotka, Oulu, Pori and Tampere and the laboratory of the Helsinki municipality, which later became that of the Helsinki and Uusimaa Hospital District), were randomised to be analysed with automation-assisted cytology. Two to five cytotechnicians from each participating laboratory were trained and licensed by the manufacturer to use the Papnet system for smear review. Since 2002 automation-assisted screening continued in the other laboratories except in the FCO laboratory in Pori.

Primary screening with an HPV DNA test was launched within the Finnish service screening in 2003, when one third of the women invited to attend the organised cervical cancer screening in seven municipalities in Southern Finland (Hyvinkää, Järvenpää, Kirkkonummi, Lohja, Porvoo, Tuusula and Vantaa) were individually randomised to be screened with Hybrid Capture 2 assay for 13 most common oncogenic HPV types. All these municipalities were using the services of one screening laboratory (the FCO laboratory in Helsinki), where the personnel was trained by the manufacturer's representative to carry out the HC 2 analysis. In the beginning of 2004, two more municipalities (Espoo and Helsinki) and another screening laboratory (the laboratory of the Helsinki and Uusimaa Hospital District) joined the study.

Randomisation of the women in the target population for the three screening arms is conducted computerised within the Mass Screening Registry of the Finnish Cancer Registry. In the randomisation process, the women's personal identifiers derived from the national Population Registry are allocated by random into the three screening arms. The information on all randomisations is centrally stored to the Mass Screening Registry and used to retain the individual random allocation at subsequent screening episodes.

4.3. Randomised screening protocols

4.3.1. Automation-assisted screening protocol

Invitations and screening visits, including smear preparation and sample-taking procedures, are organised in the automation-assisted screening arm just the same as in the conventional screening arm (see above). The only major difference between these two arms lies within the cytological analysis, which in the automation-assisted screening is conducted by using the Papnet system. The Papnet system is a neural network based device that is programmed to identify the 128 most abnormal cells and cell clusters on a conventional slide. These abnormal cells and cell clusters are brought into images that can be analysed on a normal monitor screen. Eventually, the cytological analysis is made by using manual light microscopy enhanced with the automation-assisted system. Smears analysed with automation-assisted cytology are similarly classified as conventional smears, and the criteria and procedures for management and treatment are the same.

4.3.2. HPV screening protocol

Compared to automation-assisted screening, the protocol for HPV screening differs from the conventional screening protocol in several aspects. This is essentially due to the technical differences in the primary screening tests that affect sample-taking and analysis as well as reporting the result to the woman who attended the screening.

In the municipalities that take part in HPV screening, the women targeted by organised screening programme are usually invited by a personal letter. However, a specially designed brochure containing essential information on cervical cancer epidemiology, role of HPV infection in the cancer development, purpose of cervical screening, screening visit procedures, and HPV DNA testing within the routine screening is mailed together with the invitation letter. The individual randomisation status is not shown in the invitation letter, as it would presumably affect the participation rate, but it is discussed during the screening visit to allow women to refuse from the HPV DNA test. Sample-takers of the participating municipalities are trained in HC 2 sampling and

informing the participants on the HPV screening and the implication of their individual randomisation status.

The screening visit for the women randomised for HPV screening is mostly similar to that for the women randomised for conventional or automation-assisted screening: the sample-taker fills in the gynaecological information form and prepares the VCE smear on one glass slide, and, eventually, prepares the additional HC 2 specimen. The vaginal and cervical samples for the smear are collected with the Ayre's spatulas and the endocervical sample using the special cervical sampler of the Hybrid Capture 2 test kit. After the smear is prepared, the cervical sampler is used to prepare the HPV DNA test sample, as the tip of the sampler is stored into the HC 2 transport medium tube. The tube is then labelled with the same patient information as the VCE smear. In case the participating woman explicitly refuses to take the HPV test, only the VCE smear is prepared. The screening samples and information forms are sent to the responsible screening laboratory for further processing and analysis.

In the laboratory, the HPV DNA test samples are analysed for the 13 oncogenic HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) included in the HC 2 high-risk (B) probe cocktail. The measurement is reported as the ratio of relative light units (rlu ratio) to the average of three positive controls. Samples with rlu ratio less than 1.00 are classified negative for high-risk HPV DNA and samples with rlu ratio 1.00 or higher positive for high-risk HPV DNA. The smears are stained and either screened conventionally or stored, depending on the primary HPV test result: if the HPV test result is negative (rlu ratio < 1.00), the smear is stored unscreened; if the test result is positive (rlu ratio ≥ 1.00), the cytological analysis, i.e. the cytology triage test (or reflex cytology) is made.

Only women with a positive HPV test and cytological result suggestive for dysplasia or cancer (Pap class III-V or repeated Pap class II) are directly referred for colposcopy and biopsies. The HPV positive women with normal cytology or benign cytological changes (Pap class I-II) are directed for intensified screening (new invitation in about 12-24 months) due to incident HPV infection. Within the intensified screening, women with persistent HPV infections, indicated by repeated HPV positivity, are identified and referred for colposcopy. Colposcopies and other further examinations are performed as in the conventional screening arm and the criteria for treatment are the same.

4.4. Data collection

The current study is based on the routine data from the organised cervical cancer screening programme, derived from the Mass Screening Registry of the Finnish Cancer Registry. The routine data was restricted to the years from 1999 onwards, as the randomised evaluation of new screening technologies was initiated in 1999 with the launch of automation-assisted screening, and to the laboratories and municipalities involved in the randomised screening. While this study was being prepared, routine screening data up to year 2004 was available for analysis.

In the study comparing the performance and effectiveness of screening between individual laboratories, we used the routine screening data from years 1999-2003 but also, for tentative evaluation of the screening effectiveness in the absence of adequate follow-up data, the historical incidence rates for invasive cervical cancer by laboratory area; these rates were drawn from the main database of the Finnish Cancer Registry.

Histological diagnoses were originally registered in the Mass Screening Registry database using the WHO classification. However, in the analysis we used the three-grade cervical intraepithelial neoplasia (CIN) classification, in which CIN 1 equals mild dysplasia, CIN 2 moderate dysplasia and CIN 3 severe dysplasia and carcinoma *in situ*. When appropriate, these diagnoses were further grouped into three larger categories: all CIN and cancer cases (CIN 1+), CIN 2 and more severe lesions (CIN 2+) and CIN 3 cases and cancers (CIN 3+). As the database on organised screening did not separate adenomatous lesions from squamous, however, our category CIN 3 also includes the adenocarcinoma *in situ* cases present in the data. Similarly, the numbers of invasive cervical cancer reported include both squamous-cell carcinomas and adenocarcinomas.

4.5. Statistical analysis

4.5.1. Automation-assisted vs. conventional screening

The cross-sectional validity and comparative parameters of interest, i.e. test positivity, rates of histological detection, relative sensitivity, relative specificity and positive predictive value (PPV) for screening visits in both arms were calculated by random allocation (or by intention to screen).

Test positivity was calculated by using three different cutoff levels: 1) Pap class II cytology that is an indication of intensified screening (I), 2) Pap class III cytology that is a necessary indication for colposcopy (I), and 3) referral for colposcopy on the basis of cytology (I, II). Test negativity was defined, respectively, as 1) Pap class I cytology (I), 2) Pap class I-II cytology (I), and 3) no colposcopy referral (I, II).

Relative sensitivity was measured by detection rates. Relative risks (RR) of test positivity and histological detection at various levels were estimated for the automation-assisted arm with 95% confidence intervals (CI) by using the conventional screening arm as the reference (Miettinen and Nurminen 1985). Statistical significance of differences in test positivity and the detection rates for histologically confirmed CIN and cancer between the automation-assisted and conventional screening was assessed by an asymptotic homogeneity test by using the Mantel-Haenszel chi-square test statistics (Breslow and Day 1987).

Relative specificity was assessed between the two study arms by using histologically confirmed lesions as the gold standard. The relative specificity was defined as the proportion of screening test negatives among those with no histologically confirmed lesion of a given level (including those not referred). The specificity was calculated for both screening arms by using the three different cutoff levels for test negativity (see above).

Positive predictive value was defined as the proportion of histologically confirmed lesions in test positives, and it was estimated at different cutoffs for test positivity and histological detection. Statistical significance of the positive predictive values between the study arms was tested by

using an asymptotic two-sided test for the ratio of proportions, assuming standard normal distribution (Miettinen and Nurminen 1985).

4.5.2. HPV vs. conventional screening

Test positivity, histological detection rates, relative sensitivity, relative specificity and positive predictive value for HPV and conventional screening were assessed by random allocation. In addition, test positivity and detection rates, relative risks of test positivity and CIN detection, and relative specificity were also calculated for different cutoff levels of HPV test positivity.

In comparisons by random allocation, the test positivity was defined as a referral for colposcopy and the test negativity as no colposcopy referral. When evaluating the properties of the HPV DNA testing alone (without cytology triage) with different test positivity cutoffs to conventional cytology, the HC 2 the test positivity was defined as rlu ratio equal to or higher than the given cutoff; for the conventional cytology the test positivity was defined as a decision to refer for colposcopy. Similarly, for the HC 2 test alone, the test negativity was dependent on the rlu ratio cutoff; and as regards conventional cytology, the women with no colposcopy referral were considered as test negatives.

Relative sensitivity was measured as arelative risk of CIN or cancer. RRs of colposcopy referral and histologically confirmed CIN were estimated in HPV screening arm with 95% CI using the conventional screening arm as the reference.

Relative specificity was defined as the proportion of the screening test negatives among those with no histologically confirmed lesion. For HPV screening the specificity was calculated with two definitions for test negativity: 1) cytology triage negative (i.e. no referral for colposcopy) and 2) primary screening test negative.

Respectively, PPVs were calculated for the HPV screening with two different cutoffs for test positivity: 1) cytology triage positive (i.e. referral for colposcopy) and 2) primary screening test (HPV) positive.

Relative risks of detection rates and differences in relative specificity and PPV were tested and 95% CIs estimated by assuming the observations follow a binomial test probability law (Miettinen and Nurminen 1985).

4.5.3. Variation in performance by screening laboratory

The performance by screening laboratory was measured through laboratory-specific rates for test positivity and histological detection and PPVs for histological categories CIN 1+, CIN 2+ and CIN 3+. For the analysis, the screening laboratories were coded with letters A-F in descending order of screening invitations during the study period.

Two definitions for test positivity were used: 1) recommendation for intensified screening and 2) referral for colposcopy.

The rates for follow-up smear recommendations, colposcopy referrals and histological detection were analysed with Poisson regression (McCulloch and Searle 2000). In addition to crude risk estimates, estimates adjusted for randomisation group (automation-assisted, conventional), age group (20-39, 40-49, 50-72), invitational group (five-yearly or risk group screening), and invitational year were reported with 95% CIs, by using laboratory C with the most consistent outcomes during the study period as the reference.

Positive predictive value was defined as the proportion of women with histologically confirmed lesion among the women referred for colposcopy. The association between PPV proportions and referral category was tested for all three cutoffs with an extended Mantel-Haenszel test (Mantel and Byar 1978).

5. Results

5.1. Performance of automation-assisted vs. conventional screening (I, II)

The total number of women invited for screening within the trial arms during 1999-2003 was 777,144 (II). Of these 261,754 were randomised for automation-assisted screening and 515,390 for conventional screening. A total of 548,205 women attended, 183,712 women in the automation-assisted arm (70.5%) and 362,224 in the conventional arm (70.6%). The attendance rate remained virtually consistent during the five-year study period (Table 9).

The random allocation was not followed in 15.7% of the screenings in the automation-assisted arm because of technical and logistic reasons, e.g. scanning errors or failures to get the slides scanned fast enough to maintain a reasonable turnaround time for the smears. The deviation from the assigned test decreased from 27.5% in 1999 to 8.2% in 2002 and then increased to 14.9% in 2003. The increase in 2003 was essentially due to the change of ownership in the FCO Pori laboratory, for which they were not able to continue with automation-assisted screening. In the conventional arm, automation-assisted screening was used in 0.1% of the screening visits. During the entire study period only 127 (0.03%) smears were classified as unsatisfactory, 30 in automation-assisted and 97 in conventional screening arm (Table 10).

5.1.1. Test positivity

Within the three-year data (I), the only statistically significant difference between the randomised arms was the 4% higher rate of Pap class II cytology results in the automation-assisted arm compared to the respective rate in the conventional arm. Instead, within the five-year data (II) the automation-assisted screening resulted in 8% more Pap class III findings in comparison to the conventional arm (95% CI 1.01-1.15), while no significant differences were found in the rates of Pap class II and IV-V (Table 10). During 1999-2003, roughly equal proportions of the attending women were referred for colposcopy: 0.93% of the women in the automation-assisted arm and 0.89% of the women in the conventional arm (Table 11).

Table 9 Invitations, attendance and compliance to the assigned test in automation-assisted and conventional screening arms in 1999-2003

Year	Randomised to automation-assisted screening							Randomised to conventional screening						
	Invited	Attended		Screening test used				Invited	Attended		Screening test used			
	(n)	(n)	(%)	Automation-assisted		Conventional		(n)	(n)	(%)	Automation-assisted		Conventional	
				(n)	(%) of attended	(n)	(%) of attended				(n)	(%) of attended	(n)	(%) of attended
1999	50,979	36,284	71.2	26,299	72.5	9,985	27.5	101,971	72,568	71.2	50	0.1	72,518	99.9
2000	50,377	35,477	70.4	30,101	84.8	5,376	15.2	100,631	71,173	70.7	53	0.1	71,120	99.9
2001	56,689	40,096	70.7	34,662	86.4	5,434	13.6	112,786	79,840	70.8	60	0.1	79,780	99.9
2002	55,461	38,922	70.2	35,728	91.8	3,194	8.2	110,756	77,782	70.2	39	0.1	77,743	99.9
2003	48,248	33,640	69.7	28,628	85.1	5,010	14.9	89,246	62,423	69.9	64	0.1	62,358	99.9
Total	261,754	184,419	70.5	155,418	84.3	28,999	15.7	515,390	363,786	70.6	266	0.1	363,519	99.9

Table 10 Distribution of cytological findings in automation-assisted and conventional screening arms in 1999-2003

Cytology by Papanicolaou class	Automation-assisted screening		Conventional screening		Automation-assisted vs. conventional screening	
	(n)	(%)	(n)	(%)	RR	95% CI
I	169,507	91.91	334,636	91.99	Not applicable	Not applicable
II	13,352	7.24	26,281	7.22	1.00	0.98-1.02
III	1,353	0.73	2,478	0.68	1.08	1.01-1.15
IV	171	0.09	281	0.08	1.20	0.99-1.45
V	5	0.003	13	0.004	0.76	0.27-2.13
Unsatisfactory[1]	30	0.02	97	0.03	0.61	0.41-0.92
Total	184,419[2]	100.00	363,786	100.00	-	-

Abbreviations: RR, relative risk; CI, confidence interval

[1] 113 of the 127 unsatisfactory smears derived from a single laboratory in year 2003

[2] One woman did not have her smear analysed as she was mistakenly screened according to the HPV screening protocol

Table 11 Colposcopy referrals and detected lesions in automation-assisted and conventional screening arms in 1999-2003

		Automation-assisted screening		Conventional screening		Automation-assisted vs. conventional screening	
		(n)	(%)	(n)	(%)	RR	95% CI
Referred		1,715	0.93	3,222	0.89	1.05	0.99-1.11
Histology	**CIN 1**	264	0.14	437	0.12	1.19	1.02-1.39
	CIN 2	274	0.15	498	0.14	1.09	0.94-1.26
	CIN 3	241	0.13	443	0.12	1.07	0.92-1.26
	Invasive cancer	25	0.014	49	0.013	1.01	0.62-1.63
	Any CIN or cancer	804	0.44	1,427	0.39	1.11	1.02-1.21

Abbreviations: RR, relative risk; CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIN 1, cervical intraepithelial neoplasia grade 1; CIN 2, cervical intraepithelial neoplasia grade 2; CIN 3, cervical intraepithelial neoplasia grade 3

5.1.2. Relative sensitivity

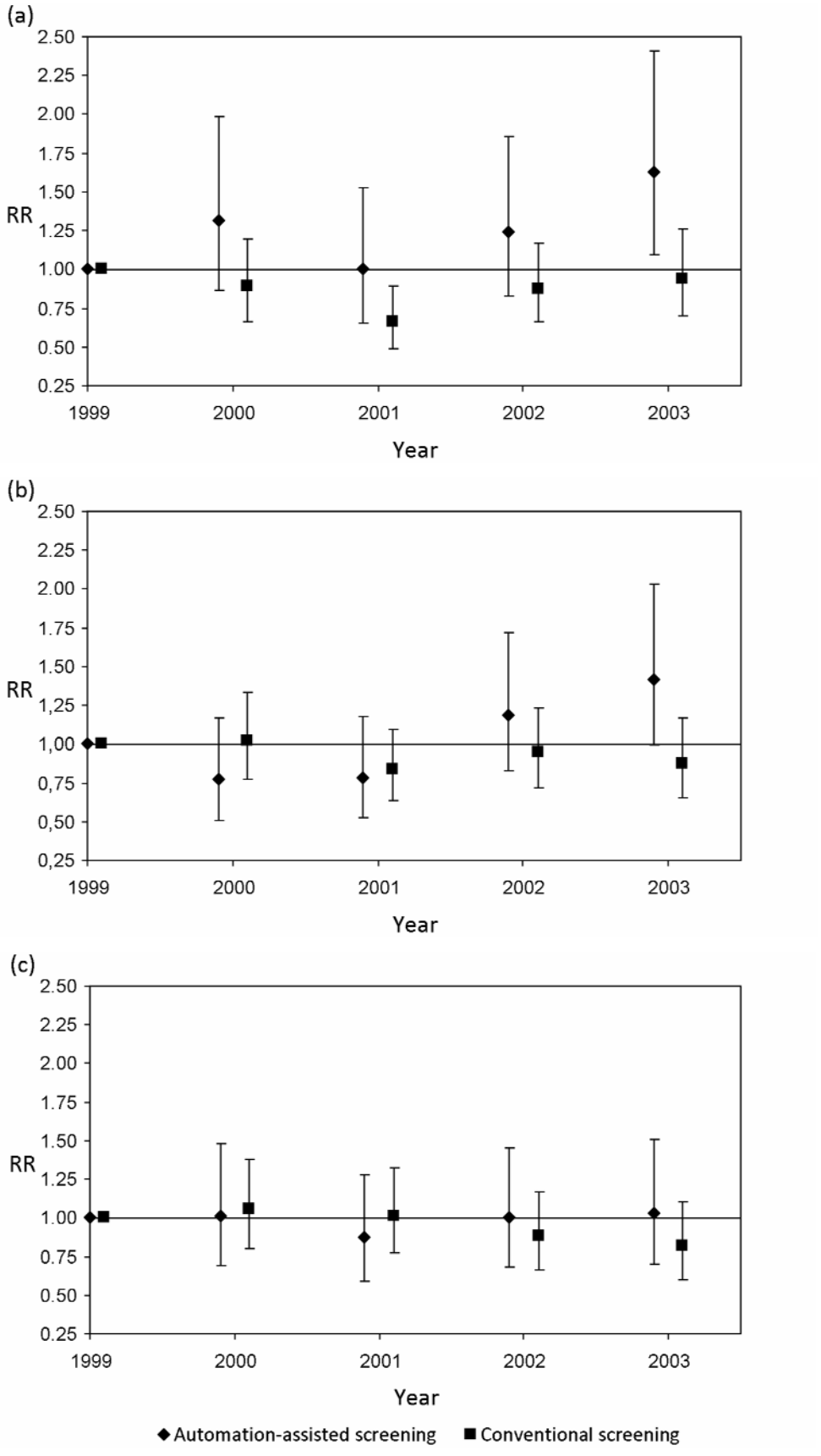
During the entire five-year study period (II), any type of an CIN lesion or invasive cervical cancer (CIN 1+) was detected in 0.44% of the women in the automation-assisted arm and 0.39% of the women in the conventional arm (Table 11). CIN 1+ lesions were significantly more common in the automation-assisted arm, RR estimate being 1.11 (95% CI 1.02-1.21) in comparison to the conventional arm. The observed difference between the arms was highest at the level of CIN 1 lesions, the detection rate of which was 19% (95% CI 1.02-1.39) higher in the automation-assisted arm. At the level of CIN 2 or more severe lesions no significant differences were observed.

The screening year was found to interact significantly with the random allocation status on histological results at the cutoff level of CIN 1+ (p-value for the interaction term 0.009, Poisson regression) (II). This was explained by an increase in CIN 1 and CIN 2 findings in the automation-assisted arm towards the end of the study period (Figure 5 a-c). For CIN 3+ no statistically significant differences were observed between the randomised arms over time (p-value for the interaction term 0.58).

5.1.3. Relative specificity

During the five-year study period (II) relative specificity estimates were exactly the same for automation-assisted and conventional screening arms. When the women with no referral for colposcopy were considered test negatives and the detection of histologically confirmed CIN 1+ was used to define the true disease status, the specificity was 99.5%. Respectively, by using CIN 2+, the specificity was 99.4% and by using CIN 3+ it was 99.2%. This was in line with the three-year data (I) when the same definition for test negativity was used: specificity for CIN 3+ lesions was 99.3% in both arms. Considering only women with Pap class I cytology as test negatives (I), the specificity estimates for automation-assisted and conventional screening were 91.7% and 91.9% respectively; and when the test negativity definition of Pap class I-II cytology was used (I), the specificity was 99.4% in both arms. Within the five-year data, as these alternative test negativity definitions were used, the observed specificities for CIN 3+ lesions were 92.1% and 99.3% respectively for both arms (unpublished).

Figure 5 Relative risks (RR) of (a) CIN 1, (b) CIN 2, and (c) CIN 3+ findings within automation-assisted and conventional screening arms in 2000-2003, in comparison to the respective frequency in 1999



5.1.4. Positive predictive value

The PPVs did not differ between the study arms (I, II). Based on the three-year data (I), 44.7% of the women referred in the automation-assisted arm and 45.0% of those referred in the conventional arm were diagnosed with CIN 1+ (RR 1.00, 95% CI 0.91-1.08). Invasive cancers were detected in 1.5% and 1.3% of the referred women, respectively (RR 1.16, 95% CI 0.61-2.20). Very similar proportions were obtained within the five-year data (Table 12, unpublished).

Table 12 Positive predictive value of colposcopy referral due to automation-assisted or conventional cytological test in 1999-2003

Histology	Automation-assisted screening		Conventional screening		Automation-assisted vs. conventional screening	
	(n)	(% of 1,715 referred)	(n)	(% of 3,222 referred)	RR	95% CI
CIN 1+	804	46.9	1,427	44.3	1.06	0.99-1.13
CIN 2+	540	31.5	990	30.7	1.02	0.94-1.12
CIN 3+	266	15.5	492	15.3	1.02	0.89-1.16

Abbreviations: RR, relative risk; CI, confidence interval; CIN 1+, cervical intraepithelial neoplasia grade 1 or more severe lesion; CIN 2+, cervical intraepithelial neoplasia grade 2 or more severe lesion; CIN 3+, cervical intraepithelial neoplasia grade 3 or more severe lesion

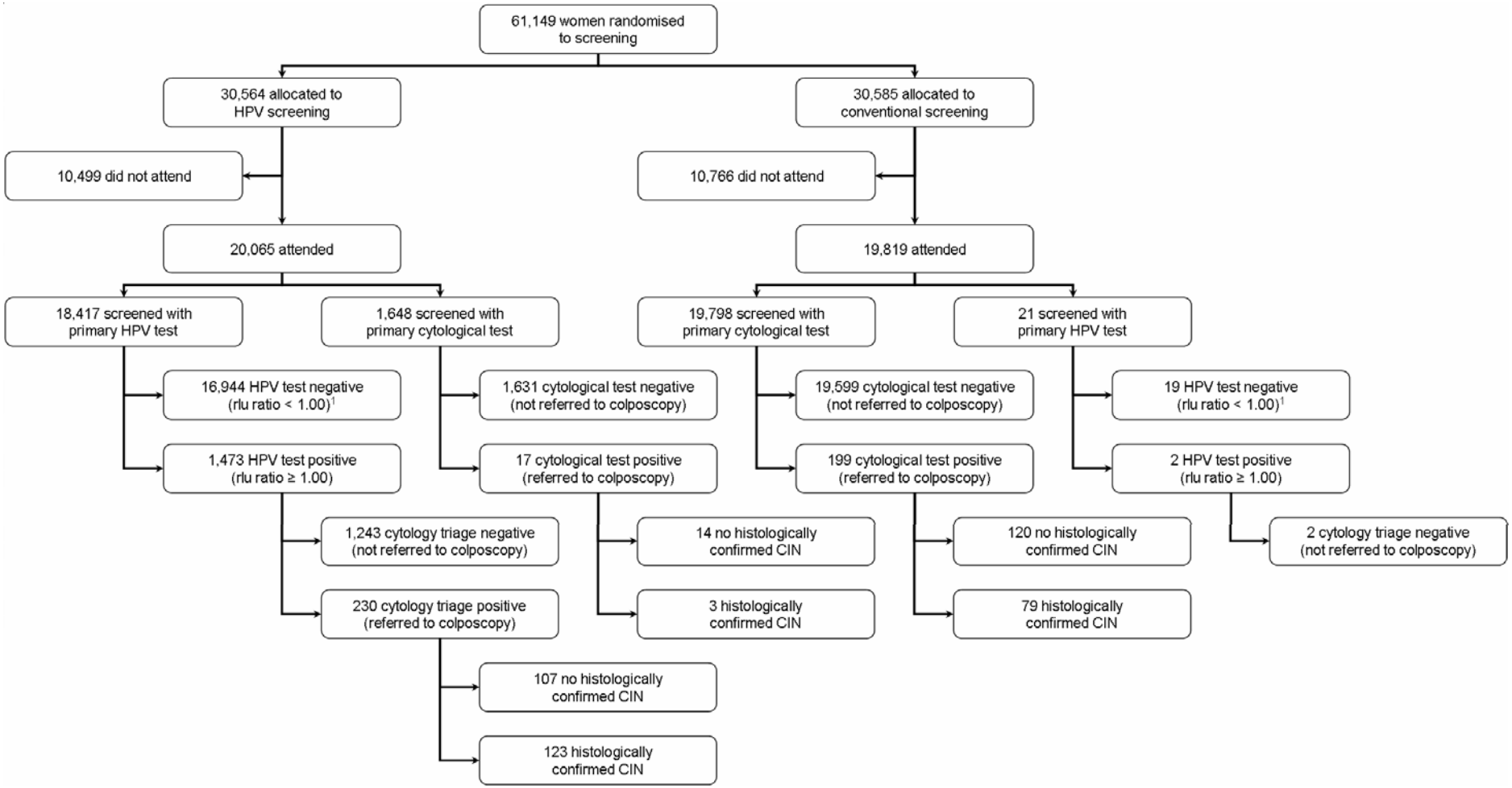
5.2. Performance of HPV vs. conventional screening (III, IV, V)

In 2003-2004, a total of 30,564 women were invited to screening in the HPV arm and a total of 20,065 screening visits (65.6%) were recorded (IV). In the conventional arm, 30,585 women were invited to screening and 19,819 attended (64.8%) (Figure 6).

Of the women who attended the HPV screening arm, 1,648 (8.2%) were screened with conventional cytology instead of a primary HPV DNA test. In the conventional screening arm, only 21 women (0.1%) were screened with a primary HPV DNA test.

HPV DNA test results ranged from rlu ratio value 0.06 to the value 4,577.59. The distribution of test results was skewed with the mean rlu ratio value of 14.80 and the median of 0.16 (Figure 7) (V). A total of 46.0% of the HPV positive (rlu ratio equal to or higher than 1.00) women had an rlu ratio under 10.00.

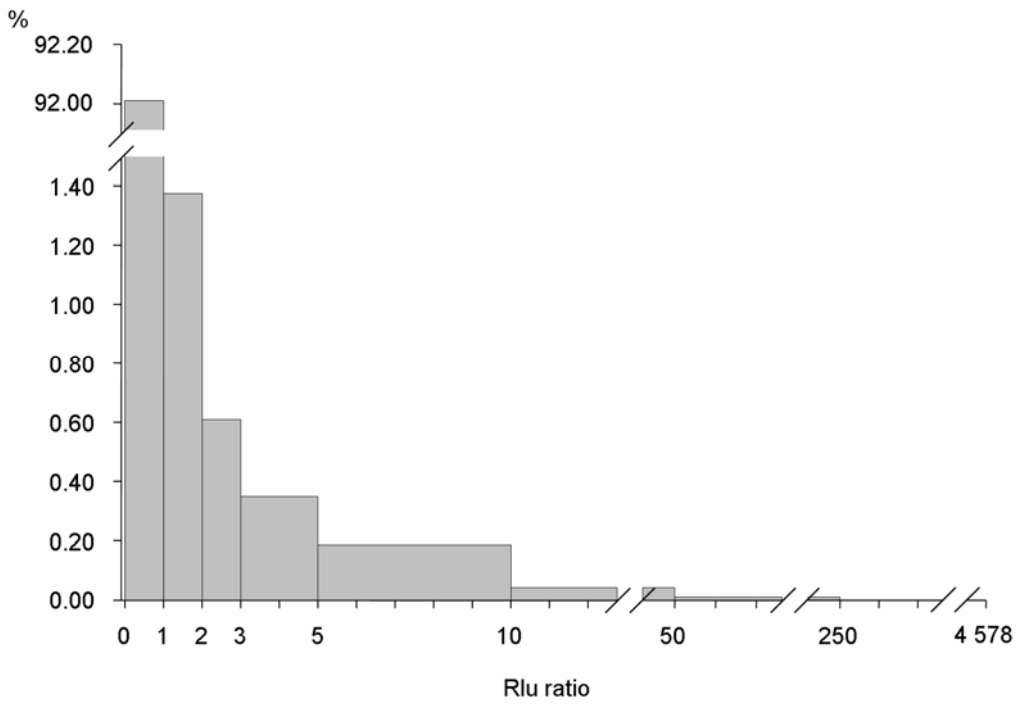
Figure 6 Flowchart for HPV and conventional screening in 2003-2004



Abbreviations: HPV, human papillomavirus; rlu ratio, ratio of relative light units; CIN, cervical intraepithelial neoplasia

[1] Of which 2,067 also had cytological test due to abnormal symptoms reported at screening visit (data not shown)

Figure 7 Distribution of HPV DNA test results by ratio of relative light units (rlu ratio) in 2003-2004



5.2.1. Test positivity

During 2003-2004, 18,417 women in the HPV screening arm (91.8%) were screened according to the random allocation, i.e. with primary HPV DNA test, and 1,473 (8.0%) of them tested positive for high-risk HPV DNA and consequently had their smear analysed (i.e. cytology triage test performed) (IV) (Figure 6). Overall, 1,490 women (7.4%) in the HPV arm had a positive primary screening test and 247 (1.2%) were referred for colposcopy. In the conventional screening arm, 201 women (1.0%) were primary screening test positives, of which 199 were referred for colposcopy. The distribution of cytological findings in the screening arms is shown in Table 13.

Based on the two-year recruitment data (IV), 23% more (95% CI 1.02-1.48) colposcopy referrals were made in the HPV arm than in the conventional arm (Table 14). This was somewhat less than estimated, based on the first-year results (51% more referrals in the HPV arm, 95% CI 3-120%) (III). Compared to conventional cytology, HPV testing resulted in 7.9 times more of test positives (95% CI 6.9-9.1) at the standard test positivity cutoff (rlu ratio 1.00) and 4.3 times more with rlu ratio cutoff 10.00 (95% CI 3.7-5.0) (V) (Table 15).

Table 13 Distribution of cytological findings in HPV and conventional screening arms by primary screening test in 2003-2004

Cytology by Papanicolaou class	Randomised to HPV screening				Randomised to conventional screening			
	Screening test used		Total		Screening test used		Total	
	HPV[1] (n)	Cytology (n)	(n)	(%)	Cytology (n)	HPV[1] (n)	(n)	(%)
I	890	1,536	2,426	12.1	18,407	1	18,408	92.9
II	369	99	468	2.3	1,180	1	1,181	6.0
III	198	10	208	1.0	157	0	157	0.79
IV	11	1	12	0.06	16	0	16	0.08
V	1	0	1	0.00	0	0	0	-
Unsatisfactory	4	2	6	0.03	38	0	38	0.19
Not available, primary HPV DNA test negative	16,944	0	16,944	84.4	0	19	19	0.10
Total	18,417	1,648	20,065	100.0	19,798	21	19,819	100.0

Abbreviations: HPV, human papillomavirus

[1] Cytology triage test performed among the HPV positive

Table 14 Colposcopy referrals and detected lesions in HPV and conventional screening arms in 2003-2004

		HPV screening		Conventional screening		HPV vs. conventional screening	
		(n)	(% of all 20,065)	(n)	(% of all 19,819)	RR	95% CI
Referred		247	1.23	199	1.00	1.23	1.02-1.48
Histology	**CIN 1**	46	0.23	24	0.12	1.89	1.16-3.10
	CIN 2	58	0.29	35	0.18	1.64	1.08-2.49
	CIN 3	19	0.10	17	0.09	1.10	0.57-2.12
	Invasive cancer	3	0.02	3	0.02	0.99	0.20-4.89
	Any CIN or cancer	126	0.63	79	0.40	1.58	1.19-2.09

Abbreviations: HPV, human papillomavirus; RR, relative risk; CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIN 1, cervical intraepithelial neoplasia grade 1; CIN 2, cervical intraepithelial neoplasia grade 2; CIN 3, cervical intraepithelial neoplasia grade 3

Table 15 Test positivity and detection numbers and rates by screening test and histological lesion

	Test positives		CIN 1+				CIN 2+				CIN 3+			
	(n)	(%)	(n)	(%)	RR	95% CI	(n)	(%)	RR	95% CI	(n)	(%)	RR	95% CI
Cytology	(Tested = 21,446)													
	216	1.01	82	0.38	1.00	-	58	0.27	1.00	-	20	0.09	1.00	-
HPV DNA test alone, using rlu ratio cutoff	(Tested = 18,438)													
1.00	1,475	8.00	123	0.67	1.74	1.32-2.31	77	0.42	1.54	1.10-2.17	22	0.12	1.28	0.70-2.34
2.00	1,221	6.62	123	0.67	1.74	1.32-2.31	77	0.42	1.54	1.10-2.17	22	0.12	1.28	0.70-2.34
3.00	1,110	6.02	121	0.66	1.72	1.30-2.27	77	0.42	1.54	1.10-2.17	22	0.12	1.28	0.70-2.34
5.00	972	5.27	117	0.63	1.66	1.25-2.20	73	0.40	1.46	1.04-2.07	21	0.11	1.22	0.66-2.25
10.00	797	4.32	112	0.61	1.59	1.20-2.11	70	0.38	1.40	0.99-1.99	20	0.11	1.16	0.63-2.16
50.00	500	2.71	93	0.50	1.32	0.98-1.77	62	0.34	1.24	0.87-1.78	18	0.10	1.05	0.55-1.98
250.00	246	1.33	57	0.31	0.81	0.58-1.13	32	0.17	0.64	0.42-0.99	8	0.04	0.47	0.20-1.06
1,000.00	84	0.46	22	0.12	0.31	0.20-0.50	22	0.12	0.44	0.27-0.72	5	0.03	0.29	0.11-0.77

Abbreviations: HPV, human papillomavirus; CIN 1+, cervical intraepithelial neoplasia grade 1 or more severe lesion; CIN 2+, cervical intraepithelial neoplasia grade 2 or more severe lesion; CIN 3+, cervical intraepithelial neoplasia grade 3 or more severe lesion; RR, relative risk; CI, confidence interval; rlu ratio, ratio of relative light units

5.2.2. Relative sensitivity

In 2003-2004 cervical intraepithelial neoplasias and cancers were detected more often in the HPV arm than in the conventional arm (IV): RR of CIN 1+ was 1.58 (95% CI 1.19-2.09). RR of CIN 2+ was 1.44 (95% CI 1.02-2.02). At the level of CIN 3 and invasive cancer there was no significant difference in the detection rates between the arms (Table 14).

Only few cases of CIN were detected among women with low rlu ratios: up to the rlu ratio 1.99 no CINs were observed; between values 2.00 and 2.99 only two cases of CIN 1 were detected (Table 15) (V). Thus, no loss in the detection rate of CIN 1+ occurred with rlu ratio cutoff of 2.00, and for CIN 2+ lesions, none were lost with the rlu ratio cutoff 3.00. With the rlu ratio cutoff of 10.00 altogether 11 (8.9%) CINs were lost: 2 CIN 3+ (9.1%), 5 CIN 2 (9.1%) and 4 CIN 1 (8.7%) lesions. With this cutoff RRs of CIN 1+, CIN 2+ and CIN 3+ were, compared to cytology screening, 1.59 (95% CI 1.20-2.11), 1.40 (95% CI 0.99-1.99) and 1.16 (95% CI 0.63-2.16), respectively.

5.2.3. Relative specificity

Relative specificity of the HPV screening with cytology triage was close to that of the cytological screening (III, IV). Based on the 2003-2004 data (IV), the specificity estimate for CIN 1+ was 99.4% in the HPV arm, for CIN 2+ it was 99.1% and for CIN 3+ 98.8%; the respective estimates in the conventional arm were 99.4%, 99.3% and 99.1%. The difference between the arms in favour of conventional cytology was slightly bigger than was observed with the one-year data (III), based on which the specificity point estimates for CIN 1+, CIN 2+ and CIN 3+ for HPV and the conventional arms were 99.3%, 98.9% and 98.7%, and 99.6%, 99.3% and 99.2%, respectively.

Relative specificity of screening with the HPV DNA test alone, using the standard test positivity cutoff, was significantly lower than that of the HPV screening with cytology triage or of the conventional screening (III, V). With the two-year data, specificity estimates for the HPV DNA test alone ranged from 92.1% (for CIN 3+) to 92.6% (CIN 1+) (Table 16) (V). By increasing test positivity cutoff, the specificity improved slowly: with rlu ratio cutoff 3.00 estimates for CIN 1+, CIN 2+ and CIN 3+ were 94.6%, 94.4% and 94.1%; and with cutoff 10.00 96.3%, 96.0% and 95.8%, respectively.

Table 16 Relative specificity of cytology and HPV DNA test alone for CIN 1+, CIN 2+ and CIN 3+ in 2003-2004

	No referral or no CIN 1+			No referral or no CIN 2+			No referral or no CIN 3+		
	Test negative	**Specificity**		**Test negative**	**Specificity**		**Test negative**	**Specificity**	
	(n)	(%)	95% CI	(n)	(%)	95% CI	(n)	(%)	95% CI
Cytology	(True negatives = 21,364)			(True negatives = 21,388)			(True negatives = 21,426)		
	21,230	99.4	99.3-99.5	21,230	99.3	99.1-99.4	21,230	99.1	98.9-99.2
HPV DNA test alone, using rlu ratio cutoff	(True negatives = 18,315)			(True negatives = 18,361)			(True negatives = 18,416)		
1.00	16,963	92.6	92.2-93.0	16,963	92.4	92.0-92.8	16,963	92.1	91.7-92.5
2.00	17,217	94.0	93.7-94.3	17,217	93.8	93.4-94.1	17,217	93.5	93.1-93.8
3.00	17,326	94.6	94.3-94.9	17,328	94.4	94.0-94.7	17,328	94.1	93.7-94.4
5.00	17,460	95.3	95.0-95.6	17,462	95.1	94.8-95.4	17,465	94.8	94.5-95.2
10.00	17,630	96.3	96.0-96.5	17,634	96.0	95.7-96.3	17,639	95.8	95.5-96.1
50.00	17,908	97.8	97.6-98.0	17,923	97.6	97.4-97.8	17,934	97.4	97.1-97.6
250.00	18,126	99.0	98.8-99.1	18,147	98.8	98.7-99.0	18,178	98.7	98.5-98.9
1,000.00	18,253	99.7	99.6-99.7	18,287	99.6	99.5-99.7	18,335	99.6	99.5-99.7

Abbreviations: HPV, human papillomavirus; CIN 1+, cervical intraepithelial neoplasia grade 1 or more severe lesion; CIN 2+, cervical intraepithelial neoplasia grade 2 or more severe lesion; CIN 3+, cervical intraepithelial neoplasia grade 3 or more severe lesion; CI, confidence interval; rlu ratio, ratio of relative light units

5.2.4. Positive predictive value

The positive predictive value of HPV screening with cytology triage was 51.0% for CIN 1+, 32.4% for CIN 2+ and 8.9% for CIN 3+ during the two-year study period (IV). For respective histological categories PPVs of cytological screening were 39.7%, 27.6% and 10.1%. The PPV of screening with the HPV DNA test alone was markedly lower than that of the HPV screening with cytology triage or of the cytological screening (Table 17).

Table 17 Positive predictive value (PPV) of HPV screening in comparison to conventional screening in 2003-2004

Histology	Screening test positive	CIN of given grade	PPV	
	(n)	(n)	(%)	95% CI
HPV screening, cytology triage				
CIN 1+	247	126	51.0	44.6-57.4
CIN 2+	247	80	32.4	26.6-38.6
CIN 3+	247	22	8.9	5.7-13.2
HPV screening, HPV DNA test alone				
CIN 1+	1,490	126	8.5	7.1-10.0
CIN 2+	1,490	80	5.4	4.3-6.6
CIN 3+	1,490	22	1.5	0.9-2.2
Conventional screening				
CIN 1+	199	79	39.7	32.8-46.9
CIN 2+	199	55	27.6	21.5-34.4
CIN 3+	199	20	10.1	6.2-15.1

Abbreviations: HPV, human papillomavirus; CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIN 1+, cervical intraepithelial neoplasia grade 1 or more severe lesion; CIN 2+, cervical intraepithelial neoplasia grade 2 or more severe lesion; CIN 3+, cervical intraepithelial neoplasia grade 3 or more severe lesion

5.3. Variation in performance by screening laboratory (VI)

During the years 1999-2003, the attendance rate ranged from 65.7% to 78.8% by screening laboratory, being lowest in the biggest laboratories. The proportions of abnormal smears (Pap class II-V) varied between laboratories from 3.6% to 10.8%, which influenced the proportions of follow-up recommendations (range from 3.2% to 10.2%) and referral rates (from 0.45% to 1.12%). Precancers and cancer were detected in 0.19% to 0.52% of the screened women (Table 18).

Table 18 Description of the study data by screening laboratory

	Screening laboratory													
	A		B		C		D		E		F[1]		All	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Invitations	227,266	100.0	200,103	100.0	132,349	100.0	96,822	100.0	73,166	100.0	47,438	100.0	777,144	100.0
Screens	156,699	68.9	131,386	65.7	93,778	70.9	76,385	78.9	53,912	73.7	36,045	76.0	548,205	70.5
Cytology by Papanicolaou class	156,698	100.0	131,386	100.0	93,778	100.0	76,385	100.0	53,912	100.0	36,045	100.0	548,204	100.0
I	142,510	90.9	118,979	90.6	90,296	96.3	68,100	89.2	49,495	91.8	34,763	96.4	504,143	92.0
II	12,768	8.1	10,888	8.3	3,017	3.2	7,831	10.3	4,007	7.4	1,122	3.1	39,633	7.2
III	1,270	0.81	1,239	0.94	393	0.42	402	0.53	375	0.70	152	0.42	3,831	0.70
IV	145	0.09	157	0.12	69	0.07	38	0.05	35	0.06	8	0.02	452	0.08
V	5	0.00	10	0.01	0	-	3	0.00	0	-	0	-	18	0.00
Unsatisfactory	0	-	113	0.09[2]	3	0.00	11	0.01	0	-	0	-	127	0.02
Cytological follow-up	12, 563	8.0	10,835	8.2	2,965	3.2	7,823	10.2	4,033	7.5	1,381	3.8	39,600	7.2
Referral	1,764	1.13	1,487	1.13	538	0.57	452	0.59	531	0.98	166	0.46	4,938	0.90
Colposcopy	1,716	1.10	1,471	1.12	518	0.55	447	0.59	500	0.93	162	0.45	4,814	0.88
Other	48	0.03	16	0.01	20	0.02	5	0.01	31	0.06	4	0.01	124	0.02
Histological lesion	807	0.52	704	0.54	241	0.26	235	0.31	174	0.32	70	0.19	2,231	0.41
CIN 1	323	0.21	177	0.13	67	0.07	68	0.09	51	0.09	15	0.04	701	0.13
CIN 2	216	0.14	331	0.25	75	0.08	79	0.10	55	0.10	16	0.04	772	0.14
CIN 3	250	0.16	162	0.12	92	0.10	82	0.11	62	0.12	36	0.10	684	0.12
Invasive cancer	18	0.01	34	0.03	7	0.01	6	0.01	6	0.01	3	0.01	74	0.01

Abbreviations: CIN 1, cervical intraepithelial neoplasia grade 1; CIN 2, cervical intraepithelial neoplasia grade 2; CIN 3, cervical intraepithelial neoplasia grade 3

[1] Participated in 1999-2002

[2] All inadequate samples were collected in 2003, when they represented 0.4% of all the smears

Variation by screening laboratory in the rates of follow-up recommendations and referral rates was statistically highly significant ($p < 0.001$). Even when controlled for randomisation group, age group, invitational group and invitational year, up to 3.1-fold differences were obtained in relative risk estimates for follow-up recommendations; for referrals the differences in RR estimates were up to 2.2-fold (Table 19).

Table 19 Crude and adjusted relative risks for cytological follow-up and referral by screening laboratory, in comparison to laboratory C

Laboratory	Cytological follow-up			Referral		
	RR_{crude}	RR_{adj}	95% CI	RR_{crude}	RR_{adj}	95% CI
A	2.54	2.44	2.34-2.54	1.96	1.79	1.63-1.98
B	2.61	2.61	2.51-2.72	1.97	1.77	1.60-1.95
C	1.00	1.00	-	1.00	1.00	-
D	3.24	3.10	2.97-3.23	1.03	0.96	0.84-1.09
E	2.37	2.23	2.13-2.34	1.72	1.57	1.39-1.77
F[1]	1.21	1.16	1.09-1.24	0.80	0.79	0.66-0.94

Abbreviations: RR_{crude}, crude relative risk; RR_{adj}, adjusted relative risk; CI, confidence interval
Adjusted figures are controlled for randomisation group, age group, invitational group and invitational year
For both levels of test positivity p for RR_{adj} was < 0.001
[1] Participated in 1999-2002

Variation between laboratories in the rates of histologically confirmed lesions was also significant, but it diminished towards high-grade lesions (for CIN 1 and CIN 2 p was < 0.001, for CIN 3+ p = 0.002): at the level of CIN 1, the differences between adjusted RR estimates were up to 4.5-fold, at the level of CIN 2 up to 4.7-fold, and at the level of CIN 3+ up to 1.5-fold (Table 20).

PPV estimates for the histological cutoff of CIN 1+ were between 32.8% and 52.0%, for CIN 2+ between 23.2% and 36.9%, and for CIN 3+ between 12.8% and 23.5% (Table 21). Variation in these estimates by laboratory was statistically significant ($p < 0.001$).

Table 20 Crude and adjusted relative risks for CIN 1, CIN 2 and CIN 3+ by screening laboratory, in comparison to laboratory C

Laboratory	CIN 1			CIN 2			CIN 3+		
	RR_{crude}	RR_{adj}	95% CI	RR_{crude}	RR_{adj}	95% CI	RR_{crude}	RR_{adj}	95% CI
A	2.89	2.65	2.04-3.45	1.72	1.58	1.21-2.05	1.62	1.49	1.18-1.87
B	1.89	1.69	1.27-2.24	3.15	2.60	2.02-3.35	1.41	1.18	0.92-1.50
C	1.00	1.00	-	1.00	1.00	-	1.00	1.00	-
D	1.25	1.16	0.83-1.63	1.29	1.24	0.90-1.70	1.09	1.05	0.79-1.40
E	1.32	1.22	0.85-1.76	1.28	1.19	0.84-1.69	1.20	1.11	0.81-1.51
F[1]	0.58	0.59	0.34-1.03	0.56	0.55	0.32-0.94	1.03	0.98	0.67-1.42

Abbreviations: CIN 1, cervical intraepithelial neoplasia grade 1; CIN 2, cervical intraepithelial neoplasia grade 2; CIN 3+, cervical intraepithelial neoplasia grade 3 or more severe lesion; RR_{crude}, crude relative risk; RR_{adj}, adjusted relative risk; CI, confidence interval

Adjusted figures are controlled for randomisation group, age group, invitational group and invitational year

For CIN 1 and CIN 2 p for RR_{adj} was < 0.001, for CIN 3+ p = 0.002

[1] Participated in 1999-2002

Table 21 Positive predictive values for CIN 1+, CIN 2+ and CIN 3+ by screening laboratories

Laboratory	Referral	CIN 1+		CIN 2+		CIN 3+	
		(n)	(%)	(n)	(%)	(n)	(%)
A	1,764	807	45.7	484	27.4	268	15.2
B	1,487	704	47.3	527	35.4	196	13.2
C	538	241	44.8	174	32.3	99	18.4
D	452	235	52.0	167	36.9	88	19.5
E	531	174	32.8	123	23.2	68	12.8
F[1]	166	70	42.2	55	33.1	39	23.5

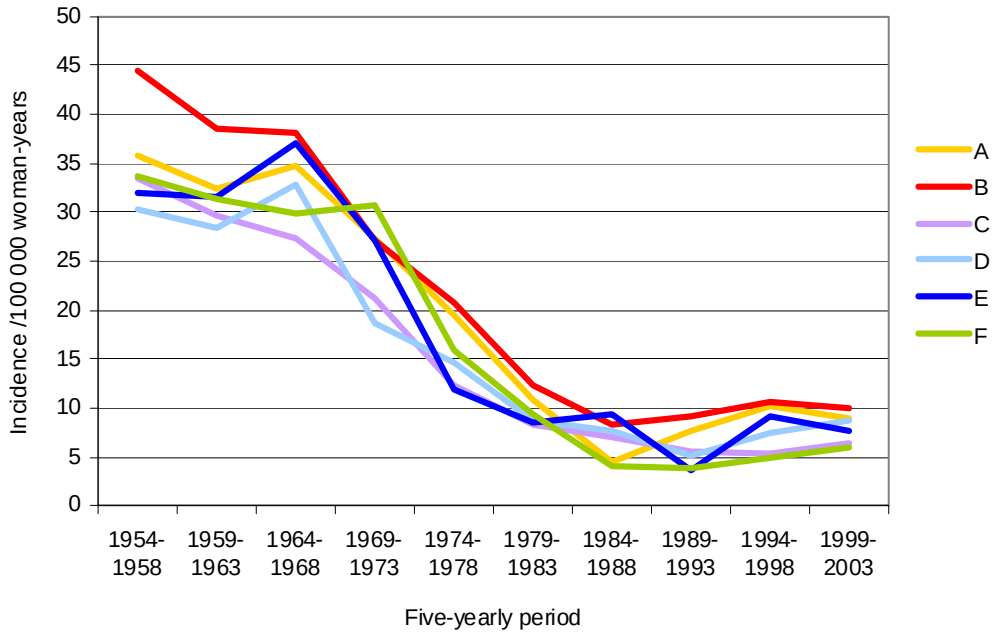
Abbreviations: CIN 1+, cervical intraepithelial neoplasia grade 1 or more severe lesion; CIN 2+, cervical intraepithelial neoplasia grade 2 or more severe lesion; CIN 3+, cervical intraepithelial neoplasia grade 3 or more severe lesion

For all histological cutoffs p was < 0.001

[1] Participated in 1999-2002

Before the organised screening started in Finland, the five-yearly average incidence rates for invasive cervical cancer among 30- to 64-year-old women varied between screening laboratory areas from 44.4 to 30.2 per 100,000 woman-years, i.e. there was maximally a 1.5-fold variation in the observed rates (Figure 8). Since the launch of screening, a proportionally uniform decrease in cervical cancer incidence occurred in all screening laboratory areas studied.

Figure 8 Cervical cancer incidence rates among 30- to 64-year-old women in 1954-2003 by laboratory area



The correlation in the rates of historical cervical cancer incidence and the detected CIN 3+ lesions by screening laboratory was high, supporting the hypothesis that the observed differences between these laboratories were mainly explained by local differences in the background incidence of cervical cancer.

6. Discussion

6.1. Comparison of the results to other studies

6.1.1. Automation-assisted screening

Large-scale randomised studies evaluating new technologies in primary cervical cancer screening are few. On automation-assistance, the Finnish study is the most extensive in the world. Like most of the studies on automation-assistance (Michelow *et al.* 1997, Doornewaard *et al.* 1999a, Doornewaard *et al.* 1999b, Duggan 2000, Nieminen *et al.* 2003, Irwig *et al.* 2004), our cross-sectional results based on more than 777,000 invitations and nearly 550,000 screening visits (II) suggest that the technology used is equal rather than superior to conventional screening; the small differences observed in the cytological and histological detection between the screening arms are unlikely to have any major clinical importance. Thus, it is clear that automation-assistance, at least in the form of the specifically studied technology, can be successfully used for primary cervical cancer screening. Whether the incorporation of automation-assistance into primary cervical screening has any benefits over the conventional screening is likely to depend on the costs and productivity of the automation-assisted technology in relation to conventional cytology (PRISMATC Project Management Team 1999, Arbyn *et al.* 2008a). In this sense, the situation with automation-assistance is very similar to that with LBC, the performance of which has proved equal to conventional cytology (Davey *et al.* 2006, Ronco *et al.* 2007b, Arbyn *et al.* 2008b), with the exception of a smaller number of unsatisfactory smears observed in some countries (Arbyn *et al.* 2008a). As LBC technologies are substantially more expensive than conventional cytology, the use of LBC has been estimated to be cost-effective only in screening programmes with high numbers of unsatisfactory smears (Giorgi-Rossi *et al.* 2007).

The preliminary results regarding automation-assisted LBC, i.e. the second generation of automation-assisted screening technologies, do not seem very different from the early results on first automation-assisted technologies based on conventional cytology (Cengel *et al.* 2003, Biscotti *et al.* 2005, Bolger *et al.* 2006, Dziura *et al.* 2006, Chivukula *et al.* 2007, Miller *et al.* 2007, Roberts *et al.* 2007, Papillo *et al.* 2008). It is quite possible that the cost-effectiveness of automation-

assisted LBC is, like that of older automation-assisted technologies, ultimately determined by the balance between costs and productivity (Biscotti *et al.* 2005, Bolger *et al.* 2006, Roberts *et al.* 2007, Schledermann *et al.* 2007).

6.1.2. HPV screening

Our results on primary HPV screening are, although based on a randomised and relatively large-scale routine screening experiment, very preliminary for estimating the cancer outcome. Thus far our results (III-V) are in line with the general observation that HPV DNA testing has higher cross-sectional sensitivity and lower specificity than conventional cytology for CIN lesions (Cuzick *et al.* 1999, Arbyn *et al.* 2006, Cuzick *et al.* 2006, Davies *et al.* 2006, Ronco *et al.* 2006a, Ronco *et al.* 2006c, Koliopoulos *et al.* 2007, Mayrand *et al.* 2007, Ronco *et al.* 2007a, Ronco *et al.* 2008). However, contrary to the Swedish randomised HPV screening study (Naucler *et al.* 2007), our results (III, IV) clearly suggest that the increase in CIN detection in the HPV screening is almost completely due to increased detection of mild- and moderate-grade precancers (CIN 1 and 2), not severe precancers (CIN 3) with higher progressive potential. Worldwide, the first follow-up results from randomised HPV screening studies, the Swedescreen and POBASCAM trials, suggest that CIN 3+ lesions are detected earlier with HPV screening than with conventional cytological screening, which may indicate higher screening effectiveness over many screening rounds and allow lengthening of the screening interval (Bulkmans *et al.* 2007b, Naucler *et al.* 2007). More recently, very similar conclusions were reached by Dillner *et al.* on the basis of pooled European data from seven primary HPV screening studies (Dillner *et al.* 2008a). Whether the clinically significant lesions are detected earlier also in the Finnish cervical cancer screening programme with primary HPV testing, will be assessed during the follow-up of the study cohort for invasive disease.

Analogously to our results on precancer detection with HPV screening, the small (11%, 95% CI 2-21%) increase in CIN 1+ detection observed with automation-assisted cytological screening in comparison to conventional cytological screening was due to increased detection of low-grade cervical lesions (II). There are several possible explanations for the increased detection of primarily mild- to moderate-grade lesions with the use of new screening technologies, as observed in our studies (II, III, IV). First, it is possible that the non-blinded incorporation of new technologies

affects the criteria for cytopathologic and histopathologic interpretation and/or colposcopy performance, for which more diagnoses of mild- to moderate-grade lesions are made. Also, a new technology itself may be more sensitive than the conventional cytology to detect mild- to moderate-grade precancers. Furthermore, the sensitivity of conventional cytology for CIN 3+ lesions may be so high at the baseline, as is the case with the Finnish organised screening programme, that only marginal increase can be achieved with any new technology incorporated. However, whatever the cause may be, the increased detection of CIN 1 and 2 lesions with new technologies is quite likely to lead to unnecessary colposcopies and treatments; also other screening-related disadvantages, such as patient anxiety, treatment-induced complications in future pregnancies and overall screening costs are prone to increase. On the other hand, increased precancer detection may also be beneficial to some extent: an earlier study shows that after CIN treatment the risk of developing cervical cancer later is equally high for CIN 1, CIN 2 and CIN 3 (Kalliala *et al.* 2005), for which the CIN treatment may affect subsequent cervical cancer incidence over a very long period of time. Therefore, with the currently available cross-sectional data we cannot rule out the possibility that finding more mild- and moderate-grade cervical lesions now may be followed by a decrease in invasive cervical cancer incidence in the future.

In our studies (III, IV) follow-up test recommendations and colposcopy referrals were made somewhat more often in the HPV vs. the conventional screening arm, whereas the number of cytological analysis decreased by more than 84% and a higher proportion of the analysed smears represented cytological abnormalities (22.1% vs. 6.8%). Overall, the proportion of screened women with any cytological abnormality was 3.4% in the HPV arm and 6.8% in the conventional arm. The most common reason for follow-up test recommendation in the HPV screening arm was a positive HPV DNA test result and the second most common reason was equivocal cytology; in the conventional screening arm the follow-up recommendations were mostly due to mild cytological abnormalities. Due to these differences in the follow-up recommendations, it is likely that the risk of cervical cancer among the women recommended for a follow-up test is different in the two screening arms; also this may eventually have an impact on the effectiveness of primary HPV vs. conventional screening.

Compared to other randomised screening studies with HPV DNA testing, our study on HPV vs. conventional cytological screening is the first nested in the routine screening programme and it is

among the first based on primary HPV DNA testing alone. In addition to Finland, HPV DNA testing has been studied as the only primary screening test in India and Italy (Sankaranarayanan *et al.* 2004b, Sankaranarayanan *et al.* 2005, Ronco *et al.* 2006a, Ronco *et al.* 2006c, Ronco *et al.* 2007a, Ronco *et al.* 2008); in the Italian trial also the use of cytology triage has been evaluated. In addition to our study (III, IV), also this Italian study showed that the number of women referred for colposcopy due to HPV screening can be reduced with the use of cytology triage close to the level of conventional cytology (indicated in the Italian study by PPV values close to each other), while the high sensitivity of primary HPV screening is utilised. Currently, the benefits of cytology triage in primary HPV screening are becoming more widely noted (Cuzick *et al.* 2006, Mayrand *et al.* 2007) and, very recently, HPV screening with cytology triage has been described as the potential state-of-the-art regimen for future cervical cancer screening programmes.

Another means to increase specificity of HPV testing is to increase the cutoff level of the HPV DNA test from the standard level, which is generally optimised for use in clinical practices. Our results on this approach (V) support the observations that in population-based screening with HC 2 assay the test positivity cutoff could be increased at least to the level of rlu ratio 2.00 or 3.00 (Ronco *et al.* 2006a, Ronco *et al.* 2006c, Mayrand *et al.* 2007, Ronco *et al.* 2007a, Ronco *et al.* 2008). Theoretically, primary screening based on an HPV DNA test alone could be applicable in a setting where the resources for skilled cytological analyses are too limited to cover the need of an organised programme using a primary cytological test, but laboratory analyses can be performed in larger numbers. In this case HPV DNA testing with even higher cutoff for test positivity could be considered: a number of studies, ours (V) included, have suggested that screening with HC 2 using rlu ratio cutoff 10.00 results in estimates of relative sensitivity and specificity for CIN 2+ lesions that are close to those of conventional cytological screening of high quality (Kuhn *et al.* 2000, Schiffman *et al.* 2000, Clavel *et al.* 2001). However, the histological lesions detected at high rlu ratio values are not necessarily exactly the same as those detected with conventional cytology (Nieminen *et al.* 2004). Moreover, as lack of financial, infrastructural and manpower resources has prohibited successful cytological screening programmes in low-resource countries, it is presumable that HPV screening with the current validated methods is too technical and expensive to be feasible in these countries (Sankaranarayanan *et al.* 2004b).

6.1.3. Variation in performance by screening laboratory

Our study on variation in performance parameters by screening laboratories (VI) showed an example why cross-sectional performance parameters should not be used as surrogates of programme effectiveness or as indicators of screening quality: despite the wide variation in follow-up recommendations (up to 3.1-fold), referrals (2.2-fold) and the rates for CIN 1 and CIN 2 (up to 4.5- and 4.7-fold, respectively), the maximally 1.5-fold differences in the rates for CIN 3+ lesions were likely to be explained by differences in the background risks between laboratory areas; there was no evidence that the programme effectiveness was different between the screening laboratories. Previously, wide variation in screening results, especially in low-grade cytology, has been reported between screening laboratories in England (NHS Health and Social Care Information Centre 2005), local screening programmes in Italy (Ronco *et al.* 2006b) and European countries (Anttila *et al.* 2004). As to the reasons for the variation, however, to distinguish between the proportion related to differences in diagnostic and registration criteria and the proportion related to differences in background risks poses a challenge.

Even if the decrease in cervical cancer incidence was equal in all laboratory areas indicating similar effectiveness, the observed variation in screening performance by laboratory is likely to have an impact on other effects of screening. Due to the large numbers of women screened, especially the differences in proportions of follow-up smear recommendations (range from 3.2% to 10.2% of the screened at one screening round) concern a large number of women of whom the vast majority do no have cervical cancer or treatable precancerous lesion, and relate to the overall screening costs. As these differences in the follow-up recommendations are largely caused by variation in the cytological criteria, it is presumable that screening with a more reproducible primary test, e.g. an HPV DNA test, would result in less variable performance by the screening laboratory. However, the actual number of follow-up recommendations could even increase from the current level.

6.2. Future challenges of cervical cancer screening

Currently, in many developed countries there is a plan to vaccinate adolescent girls against HPV 16 and 18. These plans have been made on the basis of published results on short term efficacy trials on preinvasive lesions (The Future II Study Group 2007a, The Future II Study Group 2007b, Paavonen *et al.* 2007) in the hope of decreasing the burden of cervical cancer and other papillomavirus-related disease in the future. However, the population-level effectiveness of HPV vaccinations is not guaranteed: with an HPV 16/18 vaccine roughly 70% of invasive cervical cancers could be prevented in an optimal situation (Muñoz *et al.* 2004) - a proportion lower than has been prevented with an optimal screening programme - but in unselected population the decrease in the cancer incidence may be much smaller, as seen in the efficacy trials on precancers (The Future II Study Group 2007b).

The currently available HPV vaccines, if proven effective, would be most applicable in populations with no or non-effective screening, e.g. in low-resource countries. Instead, in many wealthy developed countries a major proportion of preventable cervical cancer has already been prevented with screening, for which the benefits gained with an additional HPV vaccination programme may be relatively modest compared to the incremental costs due to vaccination. In these countries, in fact, it might be more cost-effective to strengthen or re-organise cervical cancer screening than to organise and launch an HPV vaccination programme for adolescent girls using the current vaccines. Nevertheless, the effectiveness of papillomavirus vaccination has not been assessed yet, not in terms of invasive cervical cancer or by means of overall HPV-related disease burden, and the length of possible protection with the currently available vaccines is not known. Therefore, the cost-effectiveness of HPV vaccination programmes cannot be assessed.

For the time being, organised screening remains the only evidence-based method for cervical cancer control and the evaluation of new screening technologies is justifiable. It is not certain that routine cervical cancer screening with new screening technologies introduced in the market as having superior performance and validity over cytology will ultimately be more effective than cytological screening. Yet, the new technologies tend to be more costly than conventional cytology. Therefore, if the effectiveness is not clearly increased, routine cervical cancer screening with new tecnologies will easily be less cost-effective than the conventional cytological screening.

And if the number of follow-up recommendations is increased or non-progressive cervical lesions are detected and treated at increased rates, the use of new screening technologies is likely to lead to more adverse effects compared to conventional screening. As the cross-sectional process and validity parameters are not reliable as surrogates for effectiveness, the evaluation of new technologies suggested for cervical cancer screening should be based as closely as possible on the true outcome measure of programme effectiveness, which is the number of prevented invasive cervical cancers and subsequent deaths in the target population. At least before the effectiveness of new technologies vs. conventional cytology is assessed, the latter will persist as the gold standard test for organised cervical cancer screening.

Screening will remain important in cervical cancer control also in the near future: even if the current HPV 16/18 vaccines would prove effective against a proportion of invasive cervical cancers and would become included into population-based vaccination programmes, not all the women at risk of cervical cancer will be vaccinated and cervical cancers due to other HPV types will occur even among the vaccinated women. Therefore, one of the major issues in the coming years will be whether and if yes, how to combine HPV vaccination and cervical cancer screening programmes. Another future challenge of cervical cancer screening will be how to conduct the evaluation of the alternative screening technologies that are continuously emerging and withdrawn from the market: on what basis some technologies from the plenty are chosen for evaluation and how their reliable evaluation regarding long-term outcomes is ascertained. Furthermore, emphasis should also be placed on the quality of cervical cancer screening: are there obvious weaknesses that could be disclosed and who should take steps to correct them; in the presence of a highly effective screening programme, how at least the present quality can be maintained; and how the quality should be controlled in the absence of reliable short-term measures of screening effectiveness?

6.3. Strengths and limitations of the study

As the comparisons of automation-assisted and HPV screening to conventional cytological screening are conducted in an individually randomised setting within the framework of the Finnish service screening programme for cervical cancer and the results are primarily analysed by random allocation (intention to screen), most biases are avoided. However, there are some limitations in our studies.

First, the lack of blinding the primary screening test results is the most potential cause of bias, as it may have affected the noted increase in referral and detection rates via changed diagnostic criteria. However, as one of our aims is to observe, during the future follow-up, all the potential effects of the studied new technologies on cervical cancer screening programme, blinding was considered more harmful than beneficial in the long run. Second, there might be some verification bias in CIN lesions detected within the screening arms, as the histological status was available only to those referred - we did not do colposcopies on the HPV test positive but cytology negative women nor on a sample group of women with negative primary screening test result (Cuzick *et al.* 1997). Again, the reason for this lies in the overall study design: our ultimate aim is to compare programme effectiveness between the different screening technologies by comparing the interval cancer rates between screening arms. To achieve this, false-negative lesions in the screening arms need to remain undiscovered and the use of extra interventions that would remove even a proportion of them is avoided. Concerning HPV screening, taking into account the high sensitivity of the HC 2 and high specificity of the Finnish conventional cytology, the possible verification bias is likely to be small, especially at the level of high-grade lesions.

There are also some other possible limitations concerning the HPV screening alone. The applicability of our results on HPV screening may be somewhat limited by the prevalence of high-risk HPV infections, the worldwide variation of which appears large (Clifford *et al.* 2005, Franceschi *et al.* 2006). Yet, more relevant to the applicability is the skewed distribution of HPV copy numbers in the population (in our study measured semiquantitatively by rlu ratio). Essentially similar to other populations, most women in our study had a low viral load, indicated by HC 2 test result with rlu ratio less than 1.00, which is associated with low risk of CIN 3 or cancer (Bulkmans *et al.* 2007b). In our study population, the prevalence of CIN 3+ lesions was low, roughly 1 per 1,000 screened women. This is mostly explained by the relatively high age of our screened population and the long tradition of cervical cancer screening in Finland.

Concerning the automation-assisted screening, the specific technology (Papnet) we used in the evaluation is no more commercially available nor is it further developed, for which its evaluation may sometimes be considered not very useful. However, new devices and methods based on computer- or automation-assisted screening are still emerging, and our study shows an example on how they can be optimally evaluated and in due time. Obviously, there seems to be a

discrepancy between the rates of new promising screening technologies being introduced to the market and substituted with evolved methods, or withdrawn from the market, and the time required for their evaluation until outcomes relevant to public health considerations are reached. For almost any new technology in the cancer screening programme, the time needed for an optimal evaluation upon cancer outcome is nowadays approximately 15-20 years since the technology is first introduced (Anttila *et al.* 2006).

In the study on variation by screening laboratory, we estimated the effectiveness of screening by laboratory in terms of histologically confirmed CIN 3+ lesions and by comparing the CIN 3+ rates to laboratory-specific cervical cancer incidence trends. This is not an entirely optimal approach, as historical differences in screening coverage, compliance and the extent of non-organised screening activity, and potential differential fluctuations in the background risk may affect these trends. Therefore, we cannot rule out small differences in effectiveness between laboratories.

Overall, the screening information used in our studies thus far is cross-sectional and therefore it does not contain information on smears, diagnoses of CIN and invasive cervical cancer and treatments of the follow-up period. The effectiveness of screening with new technologies can be fully assessed only with long-term follow-up data with information on interval cancers. In our data there is no information on opportunistic screening, which would also be required for a truly reliable estimation of screening benefits and potential adverse effects, such as overdiagnosis and overuse of services.

However, the most important strength of the overall study design is that after a follow-up of at least two screening rounds it will eventually enable to ultimately confirm the effectiveness of the automation-assisted and the HPV screening in comparison to the conventional cytological screening. Furthermore, the results are directly applicable to the routine screening in Finland. With this ongoing study we have also demonstrated that a thorough evaluation of routine health care practices is fully viable.

7. Summary and Conclusions

Evaluation of a new screening technology should be performed as a health services research before permanently incorporating the technology into routine use. At best, the evaluation is performed randomised, within the population and screening programme in question, by which the results are directly applicable to routine use. We have designed and executed a large, randomised, population-based experiment within the organised cervical cancer screening programme in Finland, which enables the evaluation of long-term screening outcomes.

Based on the cross-sectional results, only marginal differences were observed in the performance of conventional and automation-assisted screening. These differences are unlikely to have major clinical importance.

Primary HPV screening found more CIN lesions compared to conventional cytological screening. However, mild- and moderate-grade lesions were overrepresented, which is likely to result in overtreatment since a great deal of these lesions would never progress to invasive cancer. Screening with the HPV DNA test alone caused substantial loss in specificity in comparison to cytological screening. With cytology triage the specificity of HPV screening improved nearly to the level of conventional cytology.

Also, by increasing the test positivity cutoff from the level recommended for clinical use the specificity of primary HPV screening was increased. Nevertheless, the use of cytology triage resulted in a better validity than the use of HPV DNA test alone with an increased cutoff.

The performance of a cervical screening programme varied widely between screening laboratories, but the variation in overall programme effectiveness between respective laboratory areas was more marginal and remained virtually constant from the very beginning of the organised screening activity.

Overall, in the population-based screening, the studied new technologies have shown cross-sectional sensitivities and specificities reasonably close to conventional screening and, provided

the evaluation of screening effectiveness and adverse effects is systematically organised, they both can be used as primary tests in cervical cancer screening.

In general, new screening technologies are introduced in the market with very preliminary results suggesting their superior performance and validity over some reference test, usually cytology. However, when implemented into routine, these technologies do not necessarily increase the screening effectiveness. Instead, the use of new screening technologies may lead to larger adverse effects compared to conventional screening, if more follow-up recommendations are made and non-progressive lesions are detected and treated at increased rates. Therefore, the evaluation of new technologies for cervical cancer screening should be conducted using a randomised design, and the outcome should be as close as possible to the true measure of programme effectiveness, which is the number of prevented invasive cervical cancers and subsequent deaths in the target population.

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