Health Council of the Netherlands

Population screening for cervical cancer

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : presentation of advisory report *Population screening for cervical cancer*
Your reference : PG/ZP-2.746.254
Our reference : I-191/7/KG/WvV/cn/831-O
Enclosure(s) : 1
Date : May 24, 2011

Dear Minister,

I hereby submit the advisory report entitled *Population screening for cervical cancer*. This is the second advisory report on the prevention of cervical cancer. In the first report, the Committee made recommendations concerning vaccination against human papillomavirus (HPV), the virus that causes cervical cancer. However, such vaccination does not eliminate the need for cervical cancer screening, a topic that is explored by the Committee in the present advisory report.

The Committee notes that the Netherlands has a relatively effective screening programme. There is scope for improvement in terms of increased participation and through the introduction of new techniques, such as testing for high-risk human papillomavirus (hrHPV). The advisory report contains recommendations on how these improvements might be incorporated into the Dutch screening programme. The Committee also notes that there is still limited scientific support for improved participation, and recommends that steps be taken to boost behavioural research in this area. As with the advisory report on HPV vaccination, the Committee was able to make use of two mathematical models to determine the health and economic effects of its proposals. As before, these models were developed by researchers at VU University Amsterdam and at Erasmus MC in Rotterdam. After consulting Health Council's standing committees (the Committee on Population Screening, the Standing Committee on Medicine, and the Standing Committee on Public Health), I endorse the Committee's recommendations. In addition, I would like to make the following two points:

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If you do adopt the Committee's recommendation regarding the introduction of hrHPV screening, reports on this topic may tend to give greater emphasis to the fact that the virus is sexually transmitted (as also happened in the case of vaccination against HPV). It would be most regrettable if that were to result in reduced participation. Precisely because participation is so crucial to the success of screening, it is essential that a great deal of care be devoted to the way in which these changes are communicated.

Finally, when drafting the advisory report, the Committee assumed that HPV vaccination has not yet had any impact on cervical cancer screening, as it will be about fifteen years before the first group of vaccinated women are invited to attend for screening.

Yours sincerely,
(signed)
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to:

the Minister of Health, Welfare and Sport

No. 2011/07E, The Hague, May 24, 2011

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Contents

Executive summary

The Netherlands has a good cervical cancer screening programme. Nevertheless, there are ways in which cervical cancer prevention might be improved. A new test method is available, for example; participation amongst women in certain subgroups could be increased and follow-up for screen-positive women could also be improved. In this report, the Health Council reviews developments in this field and gives advice on reshaping of the screening programme.

Cervical cancer and the associated screening programme

In the Netherlands, more than 700 women a year develop cervical cancer: 2 per cent of all new cancer cases in women. More than half of the women in question are less than fifty years old. The average five-year survival rate in the Netherlands is 67 per cent. Each year, between 200 and 250 women in our country die of cervical cancer. Without a screening programme, the figures would be at least 2 times higher.

It is estimated that, in 2005, cervical cancer cost the Dutch health care system 55 million euros. In 2008, the cost of screening for the disease was 30 million euro.

Disease causation

Cervical cancer is caused by infection with a high-risk genotype of the human papilloma virus (hrHPV), which is transmitted by sexual contact. During the course of their lives, most women (and men) will have at least one hrHPV infection. The virus is most common in the young. The large majority of infections clear spontaneously and do not lead to the development of any cellular or tissue abnormalities. However, the longer an infection persists, the greater the likelihood that changes will take place in the epithelial cells and that the precursor of cervical cancer – cervical intraepithelial neoplasia (CIN) – will develop. Because it takes about fifteen years for cervical cancer to develop and manifest itself, the disease is an ideal 'candidate' for screening.

Screening

If treatment is provided when CIN is detected, it is possible to prevent cancer. Furthermore, invasive cervical cancer can usually be treated effectively if detected early. In the Netherlands, therefore, women between the ages of thirty and sixty are invited to undergo screening once every five years. This involves having a so-called 'Pap smear test' at the GP's surgery. Smear taking is typically performed by the practice assistant and the collected sample is analysed at a pathology laboratory. The analysis technique employed is cytological; in other words, it consists of microscopic study of the sampled cells. If the cells exhibit borderline or mild abnormalities (BMD), the woman is advised to undergo two follow-up tests. If more severe abnormalities are suspected, the woman is immediately referred to a gynaecologist for diagnostic examination (colposcopy, biopsy) and, if appropriate, treatment.

By comparison with the approach taken in most other countries, the Netherlands' cervical cancer screening programme is low-key but effective. Under the Dutch system, a woman may undergo seven smear tests, whereas her counterparts in some countries may be tested more than fifty times. Despite the relative infrequency of the testing, cervical cancer is less common in the Netherlands than in most other countries.

Weaknesses of the current arrangements

Research has shown that the sensitivity of cytological screening for the detection of high-grade CIN or cervical cancer increases as the age of the subject increases. Consequently, cytology is least efficacious for the group that can potentially

derive the most prolonged benefit from effective screening, namely young women. Furthermore, cytological screening is not a particularly effective means of detecting the precursors of adenocarcinomas, which account for about 20 per cent of cervical cancer cases.

Another drawback of cytological screening is that it lacks high specificity. Relative to the number of cervical cancer cases prevented, a large number of abnormalities are detected which would never lead to cancer.

Participation rates in the existing programme are also suboptimal. For a long time, attendance has been about 66 per cent. Ultimately, five-year coverage in the eligible target population reached 79 per cent in 2008; the difference being due to smear-taking outside the screening progamme. More than half of the women who develop cervical cancer have not attended for screening, or their attendance has been sporadic. Increasing participation is therefore the best way of maximising the programme's public health benefit. Participation is low amongst younger women, women of non-western origin, women of lower socio-economic status or women who live in cities.

Follow-up compliance also requires improvement. Screen-positive women are expected to make an appointment for follow-up testing themselves. Recent research has shown that a quarter of women diagnosed with cervical cancer have experienced a long delay between their first abnormal smear test and their ultimate diagnosis, despite the existing fail safe system (a reminder sent to the non-attendees' GPs).

New techniques

HPV vaccination

In 2009, the Netherlands started vaccinating girls against human papilloma virus (HPV), the virus that causes cervical cancer. Nevertheless, screening remains very important. It is needed first to provide continued protection of the existing target group (women who have not been vaccinated). It will be another forty years before the youngest cohort of unvaccinated women reach the age at which participation in the screening programme ends. Second, screening is needed because vaccination has only just started, meaning that many women are not yet protected. It will last at least fifteen years before the first women vaccinated in adolescence reach the programme entry age. Third, the vaccine has been aimed to protect against the two high-risk types of HPV (HPV16 and 18) which

together cause about 70 per cent of all cervical cancers. Hence, administration of the existing vaccines cannot prevent all cervical cancer. Moreover, by no means all members of the target group submit to vaccination.

Liquid-based cytology

Liquid-based cytology (LBC) was developed as an alternative for the conventional Pap test. The technique increases the quality of the sample and has practical advantages. However, LBC is not demonstrably more sensitive than conventional cytology, and it has the disadvantage of increasing the number of false positives. The technique is also more expensive and not a solution for the weaknesses of conventional cytology in the existing screening programme. Moreover, the quality of cervical smears is already high in the Netherlands (1 to 2 per cent 'inadequate'), meaning that the added value provided by the new technique is modest. LBC is already widely used in the Netherlands as a primary screening method, but the Committee takes the view that the technique's adoption is neither evidence-based nor cost-effective.

Computer-aided screening

LBC makes it possible to semi-automate the screening process. However, recent research in the UK found that computer-aided screening was associated with significantly reduced sensitivity, combined with uncertainty over cost-effectiveness.

HrHPV test

Because there is a very strong causal relationship between persistent hrHPV infection and the development of cervical cancer, tests have been developed, which can detect HPV DNA. This enables all high-risk genotypes of the virus to be detected. Numerous studies have shown that hrHPV screening is a considerably more sensitive method of detecting cervical lesions than cytology. Experimental studies have shown that hrHPV screening leads to the earlier detection of and better protection against the disease. The long-term risk of high-grade CIN or cervical cancer is considerably lower following a negative hrHPV test than following negative cytology.

Although hrHPV screening is more sensitive, it is also less specific. This means that more women need follow-up examinations. The life-time risk of being referred for colposcopy increases from 3.3 to 3.5 per cent.

Self-sampling

Another new development is the availability of self-sampling kits, which enable women to take their own smear tests at home. Offering self sampling of cervicovaginal material for hrHPV testing to women who did not attend regular screening proved to be an effective method of increasing coverage in a screening programme. The added value of offering self-sampling as an alternative for a physician-taken smear to women invited for regular screening is unknown.

Recommendations: screening programme reform

1 HrHPV testing

The Committee recommends that hrHPV testing should replace cytology as the primary screening method. HrHPV testing affords better protection against cervical cancer than cytology. A switch would have no practical consequences for subjects, from whom samples would be collected by smear taking as before.

It is of crucial importance that the hrHPV test is clinically valid and reliable: various tests are available, which differ in terms of test performance. What matters is not that the chosen test is capable of detecting all hrHPV infections, but that it detects only those hrHPV infections that are associated with high-grade CIN or cancer. In June 2010, the Netherlands Pathology Society published guidelines for hrHPV test requirements and validation.

2 Cytology triage

With a view to ensuring high quality, the Committee regards triage – the sorting and selection of women whose hrHPV test results are positive – as an essential element of the screening process. To prevent unnecessary colposcopy referrals, hrHPV-positive women should not be offered colposcopy immediately but should be further stratified by means of triage testing and repeat testing. It is appropriate to use cytology for this purpose. This does not involve the subject making another visit to the GP, because either the sample used for the hrHPV test can be re-used for cytology, or a cervical smear has already been made when a scrape for screening was taken (co-collection). If cytological abnormalities ($\geq$BMD) are observed, immediate referral should follow for diagnosis and, where appropriate, treatment. If no abnormalities are observed in triage, the subject should be offered follow-up testing (cytology) at six months.

3 Screening frequency

The implementation of hrHPV testing leads to earlier detection of CIN3+ lesions. This permits an extension of the screening interval. The Committee believes that the lifetime number of screening tests should be reduced from seven to five. It is proposed that, for women between the ages of thirty and forty, the interval should remain five years; thereafter, it should increase to ten years. Hence, women would be tested at the ages of thirty, thirty-five, forty, fifty and sixty. Thirty is still regarded by the Committee as the right age for beginning cervical screening. The screening of younger women leads to a high proportion of false positive results, overdiagnosis and unnecessary treatment. Nor does the Committee see any reason to extend screening to women over the age of sixty. However, it is advisable that, if a woman's hrHPV test result at the age of forty, fifty or sixty is positive, but no abnormalities are detected in cytological triage at baseline and after six months, the woman should be re-screened after five years.

4 Promoting participation

In order to promote participation, particularly amongst subgroups whose members are currently less likely to participate, such as young or ethnic minority women, the Committee recommends first that the screening organisations should involve more GPs in the call and recall system. The response rate is highest when the GP issues the (re)invitation; the next best approach is when the GP sends a reminder to women not responding to the initial invitation (sent by the screening organisation). It is preferable that the invitation letter should include a pre-fixed, modifiable appointment. The interval before a woman who does not respond is sent a reminder should be reduced from six months to roughly six weeks.

Finally, the Committee recommends that, after three to six months, a device for self collection of cervico-vaginal material should be sent to women who do not attend regular screening. The used test kit can be send by mail to the laboratory for hrHPV testing. This safety net plan requires careful introduction and evaluation. The Committee has taken the position that at present women who would otherwise have attended for testing are inclined to ignore their invitations and simply wait for the self sampling kit. If such behaviour became established, it may impact negatively on the efficiency and effectiveness of the screening programme: some studies have found that false positives are more common in the context of self sampling than when hrHPV tests are performed on samples taken by doctors and practice assistants.

It is not clear whether there is any advantage in offering self sampling kits to the entire target group (as opposed to non-attendees only), so that women may choose to test themselves at home, rather than go to their GPs. The Committee advises conducting a regional trial with a view to establishing whether this approach is preferable to the programme design described above in terms of participation, yield of high-grade lesions and cost-effectiveness.

5 Follow-up compliance

In order to make the screening programme more effective, compliance to follow-up should be increased. The Committee recommends that the screening organizations be involved in contacting women if follow up is needed. Offering pre-fixed, changeable appointments is expected to increase attendance.

6 Cost-effectiveness

Modelling indicates that the programme design described above may be expected to prevent 75 more cases of cervical cancer and eighteen more deaths from cervical cancer than the existing programme design, without increasing the cost.

7 Implementation

The Committee recognises that the introduction of its proposed programme design will have significant implications. The recommended changes would certainly impact on the forty-plus laboratories involved in sample analysis (a few of which focus primarily on cervical cytology). Furthermore, particularly in the first five years after the introduction of hrHPV sceening, there would be more colposcopy referrals and more follow up testing of women after six months. However, the changes may be expected to have health benefits in the form of the reduced incidence of cervical cancer and false negative test results.

Chapter 1

Introduction

The Netherlands has a good cervical cancer screening programme, especially in comparison with other countries. However, there have been various developments that offer opportunities to further improve the prevention of cervical cancer. For instance, in addition to new vaccines, there are also new screening tests. The follow-up procedure for abnormal test results could also be improved. There are also opportunities to boost participation in certain subgroups (such as women aged between thirty and forty, or women of non-Western origin).

1.1 Request for advice

These developments prompted the Minister of Health, Welfare and Sport to ask the Health Council for an advisory report on 20 March 2007 (Annex A). On 10 July 2007, in response to the Ministers' request, the President of the Health Council appointed the Committee for Combating Cervical Cancer. Details of the Committee's current make-up are set out in Annex B. On 31 March 2008, at the Minister's request, the Health Council issued its first advisory report on vaccination against cervical cancer.[1] The second advisory report, this document, deals with screening.

1.2 Link between vaccination and screening

In its first advisory report, the Committee recommended that vaccination against cervical cancer be included in the National Immunisation Programme, and that such vaccination be offered to 12-year-old girls, together with a one-off, catch-up programme for girls aged from thirteen to sixteen.[1] The Minister has now adopted these recommendations.

Nevertheless, screening remains very important. This is primarily for the existing target group (women who have not been vaccinated). It will be another forty years before the youngest cohort of unvaccinated women reach the age at which participation in the screening programme ends. Secondly, screening is needed because vaccination has only just started, so many women are not yet protected. It will be another fifteen years before the first vaccinated girls reach the age at which they are eligible to take part in the screening programme. Furthermore, it will be at least as long before the vaccination programme starts to affect the incidence of cervical cancer and the abnormalities that are precursors to that disease. Thirdly, the two types of virus (HPV16, HPV18) targeted by the available vaccines are jointly responsible for about 70% of all cervical cancers. Hence, vaccination with the existing vaccines cannot prevent all cases of cervical cancer. Moreover, by no means all members of the target group will come forward for vaccination. Accordingly, the present advisory report assumes that vaccination will have no effect on screening for the time being.

1.3 Main points of special interest

The Committee expects HPV vaccination to produce long-term benefits. In the short and medium term, any gains must come from improvements to the screening programme itself, and from the development of a strategy for reaching women who are not currently using that programme. Tests for high-risk types of human papillomavirus (hrHPV) are now available. Rather than looking for the presence of abnormal cells in the smear, this tests for the presence of DNA material from hrHPV. In addition, the availability of self-sampling kits may help to boost participation. Using a self-sampling kit, women can collect a sample of their own cervicovaginal material at home, for subsequent laboratory testing for hrHPV.

1.4 Normative framework

In 1968, at the instigation of WHO, Wilson and Jungner formulated ten criteria for well-founded population screening.[2] Later, these 'principles' were further developed and adapted. In 2008, the Health Council drafted a normative framework as an aid to decision making about whether or not to introduce a screening programme.[3] The Committee has based its advisory report on this framework.

In brief, the criteria are as follows:

- screening must be directed at important health problems
- benefit: it must be established that early detection of the disorder in question can result in a significant reduction of the disease burden; such benefits must clearly outweigh the drawbacks of screening
- valid and reliable instrument: the screening method must be scientifically substantiated and the quality of the various components of the screening process must be safeguarded
- respect for autonomy: participation in screening and follow-up tests should be based on an informed and voluntary choice; provision and implementation must be consistent with patients' rights
- efficient use of resources: there must be transparency with regard to the health care resources required by the programme (and resulting from it), in terms of cost-effectiveness and justification.

The Committee attaches importance to these principles because it is aware of the discomfort (both emotional and physical) experienced by those who participate in screening. Another factor is that relatively few participants actually stand to benefit from screening – in this case through the prevention of cervical cancer and by gaining extra years of life – aside from the relief of a "negative" (favourable) screening outcome.

It should be pointed out that the framework is not a decision model that only needs boxes to be ticked in order to yield a correct conclusion. The assessment of screening remains a complex matter, one which inevitably provides scope for differing interpretations and judgments. The central requirement of a favourable balance between benefits and drawbacks involves the usefulness of screening for individual participants. The collective viewpoint will not come to the fore until someone poses the question of whether a given form of screening should be made available by the government. The question is then one of whether the

problem addressed by the screening programme in question is sufficiently important, or whether the provision of this facility can be justified in terms of cost effectiveness, and how – given that resources are limited – priorities are to be set.

1.5 Structure of this advisory report

Chapter 2 provides a summary of the burden of disease and mortality caused by cervical cancer. It also contains a description of the etiology and natural history of cervical cancer. Chapter 3 outlines the history and current structure of the screening programme in the Netherlands, and gives a summary of the current situation regarding cervical cancer screening in other countries. Chapter 4 addresses points for improvement in the screening programme. Chapter 5 discusses new technologies for cervical cancer screening, especially testing for hrHPV. Chapter 6 explores the feasibility of boosting the participation rate. The final chapter sets out the Committee's recommendations for a new design and mode of implementation for the screening programme.

Chapter 2

Disease burden and disease process

2.1 Disease burden

Incidence

Throughout the world, cervical cancer is the second most common cancer in women, after breast cancer.[4] Approximately 80% of new cases of this disease occur in developing countries (http://globocan.iarc.fr/), which do not usually conduct screening programmes. Without screening, those countries that do use this procedure would have a significantly greater public health problem than is currently the case.[5]

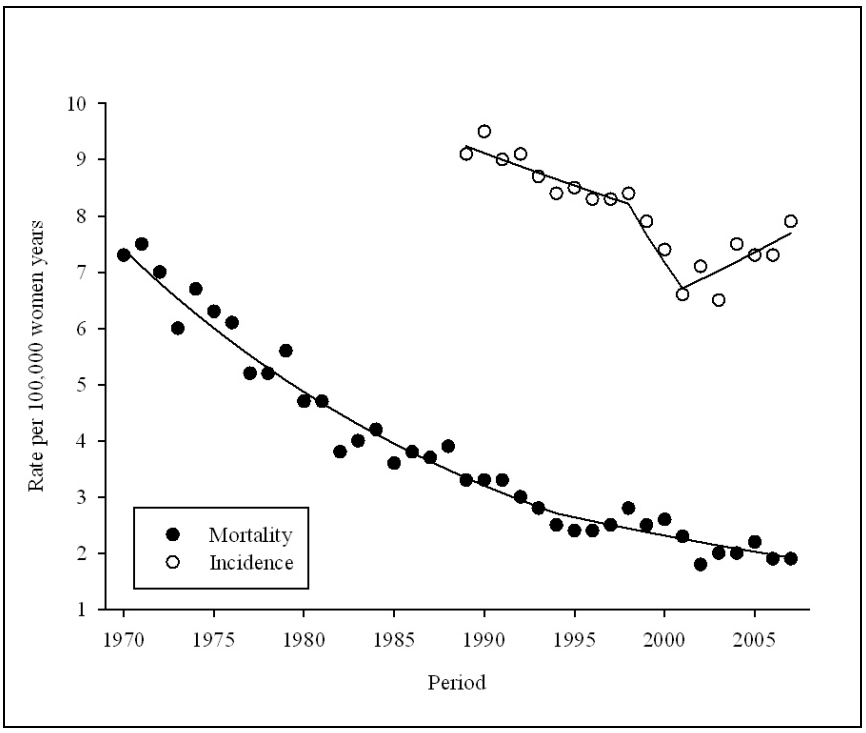
In the Netherlands, more than 700 women a year develop cervical cancer (http://nkr.ikcnet.nl), which amounts to 2% of all new cancer cases in women. More than half of the women in question are less than fifty years old. The average incidence rate (*i.e.* the annual number of new cervical cancer patients per 100,000 women) is 8.4, with incidence peaking in women between the ages of 35 and 45. This incidence rate of 8.4 corresponds to a European Standardised Rate (ESR) of 7.5 per 100,000. In this context, the Netherlands has a relatively favourable position.[6] Between 1989 (the first year that the Dutch Cancer Registration had a national data base available) and 2003, the incidence fell by nearly one third, from 9.1 to 6.5 per 100,000 women (ESR). This period of

decline now seems to have come to an end (Figure 1).[7] The incidence rate rose to 8.0, only to be followed by another fall to 7.5 per 100 000 (ESR) in 2009 (http://nkr.ikcnet.nl).

Treatment

If treatment is provided when a precursor of cervical cancer is detected, it is possible to stop the cancer itself from developing. Effective treatment is still possible if cancer has already developed but is still at an early stage. This involves excision of the transition zone between the external orifice of the uterus and the cervix.

If the disease is not detected in time, more radical treatment will be required (www.oncoline.nl). In such cases, even if the patient is cured, treatment may have lifelong repercussions in terms of infertility, sexual problems, difficulty with bowel movements and urination, and lymphoedema of the legs.



Figuur 1 Joinpoint regression analysis of the total age-adjusted incidence and mortality rates (European standardized rates) of cervical cancer in the Netherlands, 1970/1989-2007.[7]

Survival

The survival rate for cervical cancer patients depends on the extent of the disease process at the time of diagnosis. If tumour growth is still limited (micro-invasive, FIGO stage IA), then the five-year survival rate is 98%. However, if the tumour has distant metastases (FIGO stage IVB), then the five-year survival rate is just 7%. The type of tumour involved is also important. This is because adenocarcinomas have a less favourable prognosis than squamous-cell carcinomas.[8]

The average five-year survival rate in the Netherlands is 67% (http://nkr.ikcnet.nl).[9] Cervical cancer claims the lives of 200 to 250 women each year (244 in 2008, 209 in 2009; http://statline.cbs.nl). In recent decades, cervical cancer death rates declined from 3.3 per 100,000 women per year (average from 1989-1991, ESR) to 2.0 per 100,000 (average 2006-2008).

It is estimated that, in 2005, cervical cancer cost the Dutch health service EUR 55 million (www.kostenvanziekten.nl, latest information[10]). In 2008, the cost of screening for the disease was EUR 30 million.

2.2 Disease process

Cervical cancer has a protracted pre-malignant stage, which is easily recognizable for pathologists, and relatively simple to treat. These characteristics of the disease make it well suited to screening. The main types of tumour are squamous-cell carcinoma (which accounts for almost 80% of new cases of cervical cancer) and adenocarcinoma (approximately 20%[11]). In this advisory report, the Committee uses the term “cervical cancer” to cover all categories of this disease. The Committee will only draw a distinction where necessary.

2.2.1 Relation between virus and disease

In a worldwide project, HPV DNA was detected in 99.7% of cervical cancers.[12] It is generally a foregone conclusion that virtually all cases of cervical cancer are caused by an hrHPV infection.[13] It is the strongest known relationship between an environmental factor and a human cancer[14]. It is also the first necessary factor that has been shown to be linked to the development of cancer in humans. Without hrHPV, there would be no cervical cancer.[12]

There are more than 160 known genotypes of HPV. While at least thirteen HPV genotypes are carcinogenic[15] and are designated as hrHPV, there are other types that do not cause cervical cancer at all.

These findings paved the way for the development of new screening tests for cervical cancer (see Section 5.3 for more details).

2.2.2 Occurrence of HPV infections

The transmission of HPV takes place during sexual contact.[16] This is probably the only significant transmission route.[16,17] At some time in their lives, around 80% of women (and men) acquire an hrHPV infection.[18] In view of this high rate of infection, it is difficult to identify specific risk factors, other than being (or having been) sexually active. The consistent use of condoms by male sexual partners reduces the risk of viral transmission by 70%.[19] Condom use also results in fewer abnormalities in a chronic HPV infection, and more often to a complete cure ("clearance") of HPV infection. Even where abnormalities do occur, the precursors of cervical cancer show a greater tendency to regress.[20, 21]

The virus is most common in young people (Table 1).[22,23] Prevalence and point prevalence (the number of people with hrHPV at any given time) initially increase with age. In the Netherlands, it peaks at approx. 24% around the 22nd year of life, then continues to fall until the 45th year, after which it stays below a level of 3%.[22,24] Prevalence among women (aged 30-60) participating in a screening trial held in the Netherlands averaged 4% to 5% in the first round of screening and 3.4% in the second.[25,26] Repeated testing showed that, within a period of two years, half of young adults have acquired an HPV infection on at least one occasion. The risk of new infections falls with increasing age.[27]

2.2.3 HPV infections and precursors of cervical cancer

HPV infections are usually relatively short-lived, and symptom free.[28] However, mixed infections (involving different genotypes of the virus) may be more persistent. One Dutch study examined the clearance of an hrHPV type that was

Table 1 Prevalence of hrHPV infections in the Netherlands, determined using a clinically validated test (GP5+/6+-PCR). POBASCAM[22]

Age (years)	Number of women	hrHPV positive: n (%)
18-24	482	102 (21.2)
25-34	10,828	1,161 (10.7)
35-44	15,303	753 (4.9)
45-54	11,556	321 (2.8)
55-65	7,193	184 (2.6)

also found in the first study. This genotype-specific clearance was 43% within six months and 65% within eighteen months for women with cytologically normal smear.[29]

Although hrHPV infections can persist for months, in the vast majority of cases they do not cause any cellular or tissue abnormalities. However, the longer hrHPV infections persist, the greater the chance that cytological changes will occur, and that – over time – pre-malignant abnormalities of the cervix will develop.[27] In this connection, it was found that clearance was slower in women with abnormal cells in the smear (41% after eighteen months) than in women without an abnormal smear test (65% after eighteen months).[29]

The benign precursors of cervical cancer are referred to as cervical intraepithelial neoplasia (CIN). The different forms are: mild (CIN1), moderate (CIN2) and severe (CIN3) abnormalities. They are characterized by an increasing number of abnormalities in the shape and structure of the cells, relative to normal tissue. In this context, the Committee highlights the difference between screening results and CIN diagnoses. The former are determined by the cytology of smears, defined using the Pap (named after Papanicolaou) and CISOE-A classifications (Table 2). The latter are determined by the histological examination of a biopsy.

Once an HPV infection has been cleared, the associated tissue abnormalities disappear. If an HPV infection persists, it can switch from a productive infection (characterised by virus production) to a transforming infection, which leads to more extreme epithelial abnormalities. This leads to high-grade CIN. While these abnormalities too can often regress, this is not always the case. Half of all CIN2 cases show regression within two years[30], but this is less likely with CIN3.

The risk of developing CIN is related to the persistence of the infection. This was illustrated by a cohort study carried out in Costa Rica, which found that 11% women with positive hrHPV tests at first examination and one year later (+/+, persistent infection) developed CIN3 or cervical cancer (referred to here as CIN3+) within a period of three years. The corresponding rates in other groups were 1.6% in -/+ cases (a new infection), 0% for +/- (a cleared infection), and 0.3% for -/- (no hrHPV infection).[31]

2.2.4 *Precursors and cancer*

The Portland study (a prospective cohort study in more than 13 000 women over the age of thirty) investigated the ten-year risk of CIN3+ in relation to cyto-logical abnormalities and the presence of hrHPV.[32] The risk of CIN3+ was 0.8%

for women with normal cytology, 4% for ASCUS (~PAP2), and 11% for LSIL (~Pap3a1). In the case of hrHPV-positive women, the level of risk was strongly correlated to the type of virus involved. The risks with HPV18 and HPV16 were 15% and 20% respectively, compared to just 2% for other hrHPV types. [32] Other studies show that, on average, types 16, 18 or 45 cause cancer to develop at an earlier age than other types.[33-35]

The chance of regression, or the risk of progression to cancer depend on the severity of the CIN in question.[36] It is not known why progression occurs in some cases and not in others, however it is very likely related to the state of the individual's immune system.[14] The course of an infection is probably decided by the collective effect of various factors associated with the virus and the host. The risk factors for cervical cancer include smoking, multiparity, and the use of oral contraceptives for at least five years.[14,37] However, these risk factors are relatively insignificant when compared to the risk associated with persistent hrHPV infections. This association is not strong enough to enable high-risk groups to be clearly demarcated.

It is not clear what part is played by the age of the affected women. Based on screening and incidence data, Canadian researchers estimate the likelihood of spontaneous regression of CIN3 (*carcinoma in situ*) at 72% for women under the age of 40 and 47% for women between the ages of 40 and 65.[38] A New Zealand study into the fate of women who tested positive for CIN3 between 1955 and 1976, but who were not treated, showed that 31% had progressed to invasive cancer after thirty years. This would be totally unethical by today's standards, all the more so as no informed consent was involved![39] That figure rose to 50% in cases of CIN3 that had persisted for longer than this period of time. However, there was no indication that the risk involved depends on the age of the affected women. A Dutch study showed that the individual's age does not influence the likelihood of cytological abnormalities undergoing spontaneous clearance and regression.[40]

Regardless of the age of the woman in question, an hrHPV infection is usually self-limiting.[27,41] Without intervention, no more than 1% of all hrHPV infections will result in cervical cancer.[42,43] In such cases, this usually takes at least fifteen years to develop[27,42,44,45] and another four to five years before the cancer process gives rise to symptoms.[46] Cervical cancer should be considered as a late, rare complication of a chronic hrHPV infection. Given the protracted period of time taken for cervical cancer to develop, this disease is eminently suitable for screening.

2.3 Prevention

While they are undoubtedly important for various other reasons, efforts to influence risk factors such as smoking are not a viable alternative to screening. The same applies to factors that protect against HPV infection, such as condom use. In 2009, the Netherlands launched a vaccination programme for girls, to protect them against HPV infection[1]. However, many years will pass before this has the intended preventive effect.

2.4 Conclusion

Cervical cancer is a serious disease with a five-year survival rate of 67%. Partly as a result of the current screening programme, the number of new cases in the Netherlands is limited to 700 per year. Without screening, there would be a significantly greater public health problem than is currently the case.

Chapter 3

Population screening

3.1 The Dutch screening programme

3.1.1 History

This history illustrates the long and difficult road involved in establishing an effective screening programme. Many years ago, during the first half of the twentieth century, the American researchers Papanicolaou, Babes, and Traut laid the foundation of the "smear" as a test for cervical cancer. In 1954, after further refining the technique, Papanicolaou (after whom the Pap test was subsequently named) demonstrated that it was also useful for detecting the precursors of cervical cancer. Following this breakthrough, screening was introduced on a massive scale. In the Netherlands, the introduction of screening was slow and not particularly systematic.[47,48] Following the pioneering work of GPs like Brühl and Van den Dool, and the "Cyt-U-Universitair" project (1970-1973)[49], it became possible for women with health insurance to have a smear test every two years (on "medical" indication) and for the costs to be met by the Dutch National Health Insurance Funds. In the first year alone, approximately 400,000 smear tests were performed. In 1974, the Health Council recommended that a method should be developed for the systematic detection of cervical cancer.[50] The Minister of Health selected the regions of Nijmegen, Utrecht, and Rotterdam for a screening trial, with the rest of the Netherlands serving as a control group. From the end of 1975 onwards, in these trial regions, women aged between 35

and 54 received invitations every three years to have a smear test.[48,51,79] This experiment was intended to show whether a national screening programme could be both feasible and effective.

However, this plan (with a screening naive control group) was thwarted by a political decision (instigated by the Lower House of the Dutch parliament) to launch a nationwide screening programme straight away. In that framework, well over 300 000 smear tests were performed in 1981, in addition to 700,000 smear tests in the context of patient care. The Minister felt this partial overlap in terms of screening options to be undesirable, especially as young women with a low risk of cervical cancer would have to undergo frequent screening. They decided to terminate funding for the screening programme and to integrate this programme into the GP's area of responsibility.[47]

Many years were to pass before the screening programme was gradually restored. Following an organisational study and a cost-effectiveness analysis[52], the screening programme was restructured in 1996.[59] The organisational and practical aspects have since been standardised throughout the country. One of the resultant changes is that the target group's age-range has been widened to include women from thirty to sixty. The three-year screening interval has now been extended to five years.

Opportunistic screening is discouraged. Doesn't this undermine the ethical principle of respect for an individual's autonomy? The Committee does not think so, as there are good reasons for the deterrent policy. Such "spontaneous" smear tests could have added value with respect to the regular screening programme, provided that they are carried out for women at increased risk of cervical cancer. However, this does not appear to be the case.[53] This is because opportunistic screening only reaches a small proportion of the target group, primarily young women who have frequently been screened and who are therefore at low risk of developing cervical cancer (the "worried well").[54] Moreover, opportunistic screening is not set up for quality control and evaluation. This combination of factors adversely affects the balance between the pros and cons of screening. Organised screening programmes can deliver much greater health gains than opportunistic screening, at considerably lower material and intangible cost.[55-57] European guidelines therefore discourage opportunistic screening.[58]

The modifications made have enhanced the effectiveness and efficiency of population screening.[59] As a result, the number of follow-up smear tests for borderline abnormalities (Pap2) has declined from 10% to 2%.[64] Some feared that a reduction in the number of follow-up recommendations, together with a longer screening interval, might increase the risk of missing cases of cervical cancer, but this has turned out not to be the case.[60]

In 2006, responsibility for managing the screening programme was transferred from the Health Care Insurance Board (CVZ) to the Centre for Population Screening (CvB) of the National Institute for Public Health and the Environment (RIVM). On 1 January 2010, under the banner of *Versterking Infrastructuur KankerScreening* (Enhancing Cancer-Screening Infrastructure; VIKS), eighteen screening organisations were reduced to five. These new organisations conduct screening programmes for cervical cancer and breast cancer, and will soon start screening for colorectal cancer as well.

3.1.2 *Present design*

Women aged from thirty to sixty are invited to attend the screening programme once every five years. This involves a total of 800,000 women each year (www.bevolkingsonderzoeknaarbaarmoederhalskanker.nl).[61]

Screening organisations

Five regional screening organisations are responsible for implementing the programme. They receive a fee for each smear test carried out, provided that certain quality requirements are met. For example, invitations must be based on the municipal personal records database (GBA) to ensure that all women in the target group receive an invitation. The Cervix data system (CIS) is populated with data drawn from the GBA. The screening organisation selects all women whose year of birth indicates that they are eligible for a smear test. This does not include women who have indicated that they never wish to take part again, either because they do not want to or, for example, because the uterus (or cervix) has been removed.

Invitation

If the screening organisation itself issues the invitations, then the letter of invitation does not indicate a specific time and date for the screening test (which it does in the breast cancer screening programme). It is up to the women in question to make an appointment with their GP.

The screening organisation can delegate the issuing of invitations to GPs. This must be formalised in a written contract. Half of all eligible women in the country receive invitations from their own GP. GPs charged with the task of issuing invitations generate a list of eligible women, using the GP information system (HIS). Based on three parameters (date of birth, postcode, and house

number), women on the screening organisation's GBA list are matched against the GP's HIS list. Women whose names appear on both lists receive an invitation from their GP, unless the latter feels that this is either not yet necessary or no longer necessary, for instance because the woman in question is pregnant or because her uterus (or the cervix) has been removed.

GPs who issue the invitations themselves receive a fee for each woman that they invite. Women are discouraged from having smear tests performed in the absence of any medical indication, outside the context of the screening programme (opportunistic screening). The costs of such smear tests are not reimbursed within the screening programme.

Enclosed with the letter of invitation is a laboratory form and a leaflet containing information about the test. Women who fail to respond to an invitation are sent a written reminder after six months. The letter of invitation, information leaflet, and "non-participation form" (which women can use to opt out temporarily or permanently) conform to a national standard. The content has not been tailored to women from ethnic minorities. The letter and leaflet are available on the internet, in Dutch, Arabic, English and Turkish. These documents are phrased in plain, simple language.

Public information

The CvB has explored ways of providing adequate and balanced information on screening programmes for breast cancer and cervical cancer.[62] This information has been updated in accordance with a qualitatively and quantitatively tested proposal. The letter of invitation, leaflet, and results forms have been tested for comprehensibility. Based on Irwig's model of patient information (BMJ 2006;332:1148-50), the CvB's website offers both "basic information" for everyone and "additional information", if required (www.bevolkingsonderzoek-naarkanker.nl).

Information on cancer screening is now formulated with reference to a pre-defined framework. This framework provides people with guidance on how to make informed decisions about voluntary participation in screening programmes. This is based on the concept of informed choice.[63] This concept defines a well-informed choice about participating in screening as one in which people have adequate and relevant knowledge about the test. It also states that they must have a positive attitude to the test, and must actually go ahead and take it. A decision not to proceed with the test can be described as well-informed if the individual in question has adequate, relevant knowledge, and a negative attitude towards undergoing the test, as well as not taking it.

Screening

Pap-smear screening takes place in GP practices. The task of taking a smear is usually delegated to a practice assistant. The smear is subjected to a cytological examination in a laboratory. In 1996, the CISOE-A classification for cytology reporting was introduced.[64] If borderline (Pap2) or mildly dyskaryotic (Pap3a1) cells are found then the woman in question is advised to have two follow-up smear tests (Table 2). Women with more severe abnormalities (Pap3a2+, >BMD) are immediately referred to a gynaecologist for diagnosis (colposcopy, biopsy) and, if necessary, treatment.

The first follow-up smear test was recently supplemented with a triage test for the presence of hrHPV.[65] Patients with a result of "Pap1" and a negative hrHPV test are discharged at an early stage of this follow-up procedure.

Since 2010, participants receive written notifications of their results from the screening organisations, usually five days after the laboratory results are sent to their GP. This gives GPs an opportunity to contact their patients, in order to inform them personally about their test results.

Screening results

In 2008, 550,000 women attended screening. All in all, more than 5% of the participants were found to have abnormal results. Of these, the smear was unsuitable for assessment in 1.9% of cases and had to be repeated after six

Table 2 The Dutch CISOE-A classification [a)] for cytology reporting ,and referral and follow-up schedule.[59,60]

Pap	CISOE-A[a]	Description	Advice
Pap0	A3	inadequate	repeat after 6 weeks
Pap1	S1, E1-2, O1-2	normal	repeat after 5 years (next sreening round)
Pap2	S2-3, E3, O3	atypical cells (borderline dyskaryosis)	follow-up cytology at 6 and 18 months; referral if ≥Pap2 [b]
Pap3a1	S4, E4-5	mild dyskaryosis	follow-up cytology at 6 and 18 months; referral if ≥Pap2 [b]
Pap3a2	S5, O4-5	moderate dyskaryosis	direct referral
≥Pap3b	S6-9, O6-8, E6-9	severe dyskaryosis	direct referral

[a] the letters C (composition), I (inflammation, S (squamous), O (other and endometrium), and E (endocervical cylindrical epithelium) are used to indicate the composition and morphology of the smears. The letter A (adequacy of the smear) does not affect the advice, except for inadequate smears (A3).

[b] as an alternative for cytology triage an option is to combine cytology with hrHPV testing.[60,61]

weeks. The management recommendation for a further 2.5% was that they return after six months for a follow-up smear test. Finally, 0.7% were advised to consult a gynaecologist immediately for further testing and examination.[61,67] Twenty-three percent of those women who were given a management recommendation of a repeat smear test at a later date were ultimately referred to a gynaecologist anyway.[68] This brings the total referral rate to 1.3%.

The detection rate of histological abnormalities (CIN or invasive cancer) was 5.3 per 1000 participants. Sixty percent of the women who were referred directly were subsequently diagnosed with CIN3+, and another 17% with CIN2. [67]

Quality assurance, assessment, scientific research

The CvB imposes quality requirements on the screening organisations by means of the conditions attached to its funding. Screening for cervical cancer must also meet certain legal requirements, such as the Population Screening Act. Details of the quality requirements and legal requirements are set out in the Policy Framework on Population Screening for Cancer (www.bevolkingsonderzoek-naarkanker.nl). An advisory committee assists the CvB with the national management and supervision of the screening programme. The members of this committee, who are appointed in a personal capacity, give advice based on their specific knowledge and expertise in the field of screening.

The screening organisations are responsible for quality assurance. A system involving the coordinating pathologists at regional level has been set up to provide quality assurance for the relevant laboratory procedures. The framework of the national screening programme includes policy guidelines for GPs and pathologists.[65,69] Computer-assisted screening is only permitted in laboratories that have passed the Dutch Society of Pathology's (NVVP) validation test (see also Section 5.2).

The role of GPs in the screening programme poses more of a challenge in terms of quality assurance. Nor are there any contracts with the GPs involved, concerning training requirements for practice assistants, for example. These GPs receive annual performance figures, which include details of the number of smears that were unsuitable for assessment. At the behest of the screening organisations, evening courses and refresher courses are organised for the practice assistants. As yet, this does not involve any certification.

The nationwide network and registry of histo- and cytopathology (PALGA) has an important part to play in the national evaluation of population screening. All pathology laboratories are linked to the PALGA network. Excerpts of all cervical smears and histological diagnoses are stored in PALGA. This data is

processed for an evaluation of the screening programme within the PALEBA project (PALGA national assessment of cervical cancer screening).

An annual evaluation of the impact of cervical cancer screening is conducted by the National Evaluation Team for Cervical Cancer Screening Programmes (LEBA).[67]

In addition to carrying out quality assurance work and organising screening programmes, screening organisations can contribute to studies aimed at improving the screening programme.[70]

3.2 Screening abroad

The screening programme could be improved by comparing it with similar programmes in other countries and by evaluating it against European guidelines.[58,71] On 2 December 2003, the Council of the European Union issued recommendations for screening for cervical cancer, breast cancer, and colorectal cancer. It was recommended that screening should only be provided in the form of an organised screening programme (involving quality assurance for each of the various sub-procedures) rather than as opportunistic screening. It was recommended that women should be no younger than 20 and no older than 30 at the time of their first cytological screening for cervical cancer.[71] Furthermore, European guidelines have been drawn up that specifically relate to the quality of cervical cancer screening.[58,72] These guidelines also emphasise the importance of organised screening programmes.

The situation was evaluated in 2007.[73,74] In that year, there were nearly 109 million women between the ages of 30 and 60 (the core group for screening, according to the European guidelines) in the EU.[71,72] In the Netherlands, this group numbers four million women.

Screening programmes or opportunistic screening

The evaluation[73,74] shows that almost all 27 EU member states have some form of cervical cancer screening. It is important to distinguish between organised screening programmes and opportunistic screening. The former at least meets the requirement that there is a well-defined target group. During each screening round, all members of this group receive a personal invitation to have a smear test. It is also based on an effective call-and-recall system, which issues another invitation if there was no response to the first. In opportunistic screening, women take a smear test as and when the opportunity arises.

Only seven EU member states had national screening programmes (Denmark, Finland, Hungary, the Netherlands, Slovenia, Sweden, and the United Kingdom). This means that only 22% of the 109 million women aged between 30 and 60 in the EU had access to a nationally organised screening programme. Estonia, Italy, and Poland were still in the early stages of setting up national screening programmes, and Portugal and Romania had plans to do so. Screening in the remaining member states is on an individual basis (opportunistic screening) rather than in the context of nationally organised screening programmes.

The evaluation[73] also shows that there is considerable variation in terms of the screening strategy used. One example of this is the screening interval. It is recommended that screening should take place no more than once every three or five years.[71] This is because the extra adverse effects produced by an increasing number of smear tests outweigh any additional benefits gained. In countries such as Germany, Luxembourg and Austria, however, where opportunistic screening is used, there is a screening interval of one year. In Flanders, an interval of three years is recommended. In practice, however, half of all cases have an interval of just one year.[75] In Belgium, smears are usually taken by gynaecologists, and are followed by colposcopy in very many cases. There, the ratio between the number of colposcopies and the number of smear tests is 1:3[75], which is much worse than in Finland (1:125) [76] and the Netherlands (1:105), for example.[61] Finland and the Netherlands use a screening interval of five years. This means that women in Finland and the Netherlands are eligible for a smear test on just seven occasions during their lives, as opposed to more than fifty times in countries that use opportunistic screening. Yet the latter countries have neither a lower incidence of cervical cancer nor lower mortality from this disease. Finland and the Netherlands, however, are among the countries with the lowest incidence and mortality rates for cervical cancer. This serves to illustrate the limited effectiveness and poor efficiency of opportunistic screening.

There is also considerable variation in terms of the target groups involved. Women in Luxembourg are eligible for a smear test from their fifteenth year onwards. The corresponding age in Belgium and Slovakia is eighteen, while in countries like Germany and Greece it is twenty. At thirty, the age of eligibility in Finland and the Netherlands is higher than in any other country. These countries use an upper age limit of sixty for this target group, like Denmark and Sweden, for example. Eleven countries have either a higher upper age limit or none at all.

Finland and the Netherlands combine the least extensive screening strategy with the lowest cervical cancer incidence and mortality rates in the EU. This favourable position cannot be accounted for by a lower frequency of hrHPV

infections than elsewhere in the EU.[23,77] Unlike the Netherlands, Finland has extensive opportunistic screening alongside its screening programme (http://www.who.int/hpvcentre/en). A total of 460,000 smear tests are performed annually, while only 270,000 women are eligible for a smear test each year.[74]

The United Kingdom, Finland, the Netherlands, and Sweden are the only countries to reach at least 70% of the target group. There are only limited opportunities for quality control and evaluation. The Netherlands is just one of nine countries which have a national screening data system in use or under development. Seven countries have facilities for linking screening files with their national cancer registry.

In summary, many international screening activities are currently in progress, some of which have been operating for more than forty years. As yet, however, only seven EU member states have national screening programmes that are in compliance with EU recommendations.[71,72] Nowhere is there a national screening programme that uses hrHPV testing as a primary screening method.

3.3 Conclusion

Compared to other countries, the Netherlands has a very effective screening programme for cervical cancer. In the next chapter, the Committee examines the issue of whether there is scope for further improvement.

Chapter 4

Efficacy, effectiveness, and efficiency of cytological screening

Cervical cancer is a disease that can be detected at an early stage, by means of a smear test. Cervical cancer is preventable. It is preceded by a long asymptomatic but screen-detectable preinvasive stage. By identifying women with these lesions treatment can prevent the development of cervical cancer or reduce a woman's risk of dying from cervical cancer.

While its effectiveness has never been demonstrated in a randomised screening trial, there is sufficient scientific evidence that screening alleviates the burden of disease and mortality resulting from cervical cancer. This is clearly shown by the results of well-designed case-control studies, for example, as well as those of cohort studies, cohort analysis, and studies of the incidence of cervical cancer after a negative smear test. It is also supported by the results of less robust studies, such as before-and-after comparisons, and ecological studies in which differences in trends in incidence and mortality rates between countries or regions are associated with differences in screening intensity.[5,11,78-84]

In this chapter, the Committee first addresses the efficacy, effectiveness, and efficiency of the current screening programme. The Committee goes on to describe the scope for further improvements to screening programmes in the Netherlands.

4.1 Efficacy

Case-control studies have shown that participation in screening reduces an individual's risk of mortality from cervical cancer by 75%.[85,86] A meta-analysis of seventeen studies gave a value for this relative risk reduction of 66%.[14] The results of one such study (in the Nijmegen trial region) gave a relative risk reduction of 78%.[87] The results of cohort studies in Finland and in the Canadian province of British Columbia also indicate that participation in a high-quality screening programme can reduce the risk of cervical cancer by about 80%.[14]

According to one Dutch study, there is an 87% lower risk of cervical cancer in the first year following a negative (or false positive) smear test. After more than six years that had fallen to 76%.[83]

Research has also shown that the preventive effect of cytological screening is age dependent, and that it increases with age.[88-90]

4.2 Effectiveness

In practice, the effectiveness of screening never achieves its full potential, as some eligible women do not participate on a regular basis. An overview based on individual patient data (a so-called IPD meta-analysis) on participants in twelve separate studies showed that "being screened on at least one occasion" reduced the risk of squamous cell carcinoma by 54% and the risk of adenocarcinoma by 32%.[91]

If a screening programme is well organised, this will be reflected in its level of effectiveness. In the United Kingdom, for example, the incidence of cervical cancer had remained stable at a level of 14-16 per 100,000 women, even after many years of screening. However, following the introduction of a call-and-recall system in 1988, this fell by 35% within the space of just a few years.[92]

In the Netherlands, mortality from cervical cancer has been falling since 1962, fourteen years before screening programmes were launched in three trial regions.[79] Mortality has declined by well over 60%, half of which is probably due to screening and to treatment of the precursors and early-stages of cervical cancer.[93]

The incidence of cervical cancer in the Netherlands fell from 9.1 per 100,000 women in 1989 to 7.5 per 100,000 in 2008 (ESR).[94] However, this decline was due purely to a decrease in squamous cell carcinoma. The incidence of adenocarcinoma remained the same,[11] regardless of age.[95] Accordingly, the proportion of adenocarcinomas in the total number of new cases of cervical

cancer rose from 16% to 21% between 1989 and 1998.[11] Other countries with long-standing screening programmes, such as Iceland and Sweden, also showed a decreasing incidence of squamous cell carcinoma associated with a stable or even rising incidence of adenocarcinoma.[96-98] This shows that cytological screening is not particularly effective at preventing adenocarcinomas (see also Section 4.4.3).

Estimates that are partly based on model calculations show that the Dutch screening programme prevents 330 cases of cervical cancer each year, and that 175 fewer women are dying from this disease.[99] This is a conservative estimate, based on the assumption that women who do not participate in screening programmes have a three times greater risk of developing cervical cancer than those who do participate. Calculations based on a smaller difference in risk indicate that screening has a considerably greater preventive effect. Accordingly, calculations for England and Wales show that, in the absence of screening, there would have been over 3,000 deaths from cervical cancer (in 2002, the actual figure was 1003), rising to approximately 5,500 deaths in 2030.[5]

4.3 Efficiency

An important measure of efficiency is cost- effectiveness. The "cost-effectiveness of screening" refers to the net cost (the cost of the screening programme minus the savings in diagnosis and treatment arising from the prevention of disease), expressed per life year gained, and preferably adjusted for quality of life (QALY). Costs (in the general sense) must first be incurred before any associated health gains and savings can be achieved. Any costs or effects that do not appear immediately, but at some time in the future, are discounted.[100] Discounting means that the valuation of costs and effects depends on the time at which they occur. Effects are discounted because people generally prefer to enjoy beneficial effects as soon as possible, while postponing adverse effects for as long as possible. The costs and effects of a screening programme are discounted at a given rate (expressed as a percentage). The exact level of this discount rate is a matter of debate.[100,101] The Committee's working assumption involves a theoretical discount rate of 1.5% per year for effects and 4% for costs.[102] In the interests of comparability with other cost-effectiveness analyses, the Committee has also reported results involving a discount of 3% for both costs and effects.

When set against a situation in which there is no screening at all, the cost effectiveness of the current cervical cancer screening programme is relatively poor compared to that of screening programmes for breast cancer[103] or colorectal

cancer, for example.[104] Its cost effectiveness is estimated at EUR 5,900 per QALY. However, it is favourable when compared to the cost effectiveness of vaccination against HPV[1], and is still well below the commonly used limit value of EUR 20,000 per QALY.

Moreover, since the 1996 reorganisation, there has been an improvement in effectiveness.[59,93,105,106] Participation has increased, the target group's age-range has been expanded, and follow-up after an abnormal smear test has improved. Also, many fewer repeat smear tests and opportunistic smear tests have been performed. However, the organisation costs are higher than previously estimated, and the laboratory costs are outpacing inflation. Moreover, since 2006, hrHPV tests have been increasingly added to follow-up smear tests, as triage.[26,107] Nevertheless, the cost-effectiveness ratio has improved since 1996.[93, 108]

4.4 Opportunities for improvement

While the Dutch screening programme is well designed, the Committee feels that there are still significant opportunities for further improvement.

4.4.1 Increase participation

Nothing is more vital to the effectiveness of a screening programme than the participation rate. In 2008, as in previous years, the response to screening invitations (the percentage of women participating within three to fifteen months compared to the number of women invited) was low, at 66%. This level of participation has not been adjusted to allow for women who no longer require smear tests or who have already had such tests outside the context of the screening programme (opportunistic smear tests on medical grounds). In total, 79% of the target group are reached once every five years. When calculating this "five year coverage", smear tests performed on medical grounds and opportunistic screening are included. Women whose uterus has been removed are not included in the target group (the denominator). In the interest of effectiveness, it is important to adhere to the recommended screening interval.

A subject's risk of cervical cancer depends on their smear-test history. Cervical cancer is more often diagnosed in subgroups that are less likely to participate in screening (such as women of low socioeconomic status or women below the age of 45) than in those who do participate.[109-114] A small-scale Swedish study of women who had not participated in the screening programme for more than six years found that 26% of these individuals had a positive hrHPV

test.[115] The corresponding figure in a Dutch study of non-participants was 10%.[114] This percentage is significantly higher than in participants in the standard screening programme (or screening trial) in the Netherlands (4-5%).[26,77]

Incomplete participation is the key factor in the incidence of cervical cancer.[116-120] A meta-analysis of 42 studies showed that, on average, 54% of cases of cervical cancer (all ages) occur in women who participate in screening irregularly or not at all.[121] Recent research in the Netherlands put this figure at 63%.[122] For patients aged from thirty to sixty, it was 54%.[122] Cervical cancer at an unfavourable stage was detected three times as often (49% FIGO stage IIB+) among women who had not participated fully than among those who had taken their smear tests as scheduled (within the screening interval; 16% FIGO stage IIB+).[122]

Accordingly, it is vitally important to contact those women who attend screening irregularly or not at all. In this way, the greatest health gains can be achieved. The Committee will revisit this issue in Chapter 6.

4.4.2 *Improve follow-up*

Based on the results of the smear test, a follow-up recommendation is made (Table 2, page 35). However, screen-positive women sometimes ignore them completely or wait for a long time before taking any action. [25,61,118,123] In 2008, 15% of those advised to take a follow-up smear test because of Pap2/3a1 (BMD) failed to do so (within 365 days), while the no-show rate among those advised to see a gynaecologist immediately was 11% (within 150 days). Over a four-year observation period, these percentages were 10% and 3% respectively.[107] With regard to a management recommendation of referral after repeated Pap2 (borderline dyskaryosis) in follow-up smear tests, 23% failed to comply within one year, even though the risk that they have CIN2+ is 10%.[124]

Research into the screening history of 286 women who had recently been diagnosed with cervical cancer showed that, in 26% of these cases, a great deal of time had elapsed between the first abnormal smear test and confirmation of the diagnosis. In the case of those with a management recommendation of a "follow-up smear test after six months" this involved a period of >24 months, while for "refer to a gynaecologist immediately", the interval in question was >6 months.[122]

For screening to be fully effective, all abnormal smear tests must trigger organised, effective, and well monitored follow-up. In the current situation,

women participating in the screening programme are required to make an appointment themselves after a period of six months. The pathology laboratories notify the GP just once if no follow-up test has taken place. In view of this, it might be better if the screening organisations were to become involved in issuing invitations for follow-up testing, rather than relying on the women in question to take the initiative. Without adequate follow-up, screening has little point.

4.4.3 *Reduce false-negative smear tests*

Relatively insensitive tests often produce incorrect, negative findings. In other words, they deliver many false-negative results. A false-negative test for CIN3 or cancer (CIN3+) means that the screening test delivers normal results, even though the individual in question has CIN3+.

Histopathology is the gold standard for assessing the sensitivity of cytology but, given its high degree of sensitivity for CIN3+ (see Section 5.3), the hrHPV test is also a good reference test. The first round of the POBASCAM screening trial (discussed in Section 5.3) found that, using a threshold of ≥BMD, cytology had a sensitivity for CIN3+ of 75% relative to a combination of hrHPV testing and cytology.[125] A more accurate calculation of sensitivity – based on interval carcinomas within the five years following negative cytology – stood at 64%.[126] In most other countries, sensitivity was found to be lower.[89,127,128] In one German study, for instance, sensitivity for CIN3+ was found to be just 46%, despite a very low referral threshold.[129]

The sensitivity of cytological screening depends on the age of the woman in question. According to one review study, in women above the age of fifty, cytology has a sensitivity of 79% for the detection of CIN3+, while the figure for women below the age of 35 is 52%.[89] Case-control studies also show that cytological screening provides substantially less protection against cervical cancer (stage IB or more advanced stages) in women below the age of 35 than in older women.[88, 90]

Even in the high-quality laboratories that operate in the Netherlands, some relevant precursors of cervical cancer may still go undiscovered. As previously stated, adenocarcinomas in particular are often missed by cytological screening.[88, 116, 130, 131] This is because adenocarcinomas often develop in relatively inaccessible places, in the cervical canal.[14] Furthermore, adenocarcinomas are associated with higher mortality.

Greater sensitivity should not be expected to produce miracles. A meta-analysis of 42 studies showed that 29% of all cervical cancer cases can be attributed to false-negative Pap smears.[120,121] Dutch studies give a figure of

around 15%, [117,119,132] even when only women between the ages of 30 and 60 are involved.[118, 123]

4.4.4 *Limit false-positive smear tests*

In addition to false-negative test results, screening also produces false-positive test results. Not only do these lead to diagnostic procedures, disquiet and anxiety among the women involved, they also generate substantial costs, all of which – in retrospect – is totally unnecessary. The stress caused to women, even by a borderline Pap smear result should not be underestimated. This is exacerbated by the long duration of follow up, by uncertainty about the significance of the results, and by the very nature of the follow-up tests.[133,134] Approx. 2.5% of all participants get a Pap2/3a1 (BMD) smear test result and are given a 6-month follow-up smear advice.[61] One third of those who followed this management recommendation were ultimately referred to a gynaecologist[67, 107] and CIN2+ was diagnosed in 10% of these cases.[124] This means that the management recommendation for a follow-up smear test at a later date, which is given in response to a Pap2/3a1 smear test result, has a positive predictive value (PPV) for CIN2+ of about 3%. This therefore results in many unnecessary smears, referrals, colposcopies, and biopsies.

In addition to the 2.5% of women with a six-month follow-up smear, 0.7% of the participants are referred for immediate colposcopy, and a further 1.9% are advised to repeat the smear test after six weeks because of inadequate quality of the initial smear.[61] The PPV of a referral recommendation is 53% for CIN3+ and 69% for CIN2+.[77]

4.4.5 *Limit overdiagnosis*

Overdiagnosis is at least as problematic as false-positive test results. As explained in Section 2.2.4, less than half of all cases of CIN3 that are detected will ultimately develop into cancer. However, it is not possible to predict which women will be affected.

While (over)treatment in this instance is considerably less radical than in the case of breast or prostate cancer screening, it is still harmful, due to the large numbers of people involved. Screening uncovers many cases of CIN, especially in younger women. Great care should therefore be taken when fixing the age for beginning cervical screening. Limited procedures, such as large loop excision of the transformation zone (LLETZ) [135] are usually sufficient in cases of CIN2 or

CIN3. These do not entail an increased risk of serious obstetric complications, such as perinatal mortality or extremely premature birth.[136]

It is worth noting that the issues of overdiagnosis and overtreatment are not as serious in the Netherlands as they are elsewhere. One reason for this is that women here are not invited to screening until they reach the age of 30. Another is the longer screening interval used in this country. Finally, opportunistic screening and relatively unproductive management recommendations for follow-up screening have all been significantly reduced.[59,107] However, there is still scope for further improvement.

4.5 Conclusion

Various aspects of cervical screening need to be improved:

a firstly, it is important to improve participation among specific subgroups (women aged between thirty and forty, and especially women from ethnic minorities, in urban areas, or of low socio-economic status)
b secondly, the sensitivity of the Pap smear is limited, especially in young women and for adenocarcinoma
c thirdly, follow-up procedures after abnormal screening results need to be simplified
d finally follow up needs to be monitored more effectively.

Chapter 5

New techniques

This chapter addresses various technical advances. Firstly there is liquid-based cytology (LBC) and automation-assisted reading, both refinements in the field of cytology. One advance of a very different nature is the hrHPV test.

5.1 Liquid-based cytology

Screening traditionally involves identifying morphologically abnormal cells in a smear-preparation containing cells taken from the cervix. In recent years, research has been carried out to determine whether this technique has scope for improvement. Rather than smearing cellular material directly onto a glass slide, the idea is to first fix the cells in solution before subjecting them to further processing in the laboratory. One advantage of LBC is a more representative sample, due to the greater numbers of loose cells. Other benefits are improved cell fixation, a better distribution of cells on the slide, and the option of using any residual material for further testing (triage).[137-140] These benefits could lead to a more reliable evaluation, resulting in greater sensitivity and a smaller percentage of smears that need to be repeated due to inadequate quality (Pap0, Table 2). The Committee discusses another potential benefit of LBC, computer-assisted screening, in the next Section.

The advantages seemed clear and LBC is already being widely used. In 1996, the U.S. Food and Drug Administration authorised the use of two systems for LBC. [139] The introduction of LBC in the UK was completed in 2008.[140] In the

Netherlands, LBC is already widely used as a primary screening method (without a permit, under the Population Screening Act). A survey carried out by the Foundation for the Quality Assessment of Clinical Pathology (SKKP) found that, at the end of 2008, 39 of the 53 participating laboratories (74%) were using LBC.[141]

Various reasons have been given for this large-scale introduction. In the United Kingdom, for instance, the percentage of inadequate-quality smears was much higher than in the Netherlands.[140] Another reason is that smears are easier to evaluate. These benefits are often given greater emphasis than the drawbacks of lower specificity and of the stress imposed on women by unnecessary follow-up tests.[142] These practical benefits, coupled with interim findings which indicated that LBC is not outperformed by conventional cytology, caused many laboratories to independently switch to the former method. Was this a good decision, in scientific terms?

Various meta-analyses of the initial research results (which included just a single randomised study[143]) showed that LBC's sensitivity[139, 144] and specificity[139] were no higher than those of conventional cytology. Since then, the results of four randomised trials have been published.[68,143,145-147] The findings show a consistent fall in the percentage of inadequate smears. However, given the current high quality of conventional cytology here (1.2% Pap0), LBC does not offer the Netherlands a great deal of added value in this regard. To avoid just one Pap0 result, 128 women must be screened using LBC.[145] The Nethcon trial[68, 145] and the Italian NTCC trial[143] showed that LBC and conventional cytology have comparable levels of sensitivity for CIN2+ or CIN3+. In another Dutch trial and a small Swedish trial, LBC was found to be more sensitive for CIN2+ than conventional cytology (no details were given concerning sensitivity for CIN3+), but this was accompanied by more false-positive smears.[146,147] This results in further cost increases, as additional diagnostic tests are needed. The Italian study also revealed an increase in the number of abnormal smears.[143, 148] While cases of CIN1 were detected more often using LBC, this did not apply to CIN2+ or CIN3+.[143]

The Committee has determined that LBC is not demonstrably more sensitive or specific for CIN3+ than conventional cytology. Indeed, three of the four randomised trials that have been published show that it has a lower specificity. The findings also show a consistent reduction in the percentage of inadequate smears, but this has little added value for the Netherlands. The Committee concludes that there is no scientific basis for using LBC as the primary screening test.

When the decision is taken to switch to hrHPV screening, this largely eliminates any practical benefits of LBC. If such a decision is taken, the Committee sees no objection to the use of the collection and transport medium that is employed in LBC.

5.2 Automation-assisted reading

LBC makes it possible to partially automate the screening process. Here, a scanner is used to examine the smear, and the coordinates of potentially abnormal cells are recorded. Cytodiagnostic staff can then use the computer to relocate these cells in the preparation, and determine whether they are indeed abnormal. Studies in this area are few and far between. They are mainly limited to observational studies, and do not provide very convincing evidence. However, two studies stand out, in terms of the superior quality of their design. One was an Australian study (with a split-sample design) whose results indicated that computer-assisted screening had greater sensitivity for CIN2+. The other was a large Finnish randomised trial, which gave no such indication.[149-151] However, both studies compared computer-assisted screening (of thin layer preparations) with conventional cytology. As a result, it is unclear whether any differences detected resulted from computer-assisted screening as such (as a follow-on to LBC), or from LBC itself.

In the United Kingdom, this problem was overcome in a randomised trial that used the manual evaluation of thin layer preparations as a control.[152] The results of this trial (MAVARIC) showed that computer-assisted screening as a primary screening method was significantly less (6.3%point) sensitive for CIN2+ than LBC.[153] Despite a 60% to 80% gain in productivity, computer-assisted screening was not more cost-effective.

In 2008, the Ministry of Health, Welfare and Sport decided to allow the use of computer-assisted screening at the initiative of the laboratories in question, subject to strict conditions. To this end, the Dutch Society of Pathology has established a protocol for a validation test with which laboratories must comply.[154] The protocol is used to determine whether manual screening and computer-assisted screening are being assessed in the same way. Nine laboratories have passed the validation test. Unless and until computer-assisted screening can be shown to be more advantageous than manual screening, no decision will be taken on its inclusion in the screening programme and no additional funding will be provided, as is the case for LBC.

5.3 HrHPV test

As stated in 2.2.1 the identification of an extremely strong, causal relation between a persistent hrHPV infection and the development of cervical cancer and its precursor lesions led to the development of tests for HPV DNA. All high-risk strains of the virus can be detected by this means. There are about thirty commercial tests for hrHPV. However, this advisory report focuses almost exclusively on studies involving Hybrid Capture 2 (hc2) and the GP5+/6+PCR enzyme immunoassay, or their predecessors.

HrHPV testing can be used for various purposes, such as a primary screening test, possibly in combination with cytology. It can also be used as triage for women with minor cytological abnormalities, and as a follow-up for women after treatment for CIN.[155] In this advisory report (about screening), the Committee discusses the use of the hrHPV test as a primary screening test.

5.3.1 Sensitivity

Results of a cross-sectional study

An hrHPV test is significantly more sensitive for CIN2+ or CIN3+ than a conventional (cytological) smear test. However, hrHPV screening has lower specificity.[89] The first results were derived from cross-sectional studies. This involves an investigation of test performance in a particular experimental group at a given moment in time or in a given screening round. As a result, the sensitivity of the test cannot be accurately determined. Nevertheless, its relative sensitivity can be determined, with reference to the total number of cases of CIN2+ or CIN3+ identified by hrHPV testing and cytology. The results of cross-sectional studies tend to overestimate the sensitivity of the test, as further testing is only triggered by a positive result.

According to a meta-analysis of twenty-four studies, the test's sensitivity (or relative sensitivity) for CIN2+ was 89% but varied over a large range.[155] When the meta-analysis was restricted to the eighteen studies carried out in Europe and North America, sensitivity was found to be 98% and consistently high. Other review studies[156] confirm this high degree of sensitivity.

HrHPV screening is also better at detecting adenocarcinomas.[157] Not only are these tumours associated with a more adverse five-year survival rate, but they cannot easily be detected using cytology.

Results of longitudinal studies

Sensitivity can be calculated more accurately using longitudinal studies than with cross-sectional studies, as the former allow for abnormalities that are discovered following a negative screening test. The results of observational longitudinal studies and large-scale screening trials in Europe[25, 131,158,159] and China[160], for example, confirm that the hrHPV test is substantially more sensitive than cytology. When calculated over a period of 45 months, sensitivity for CIN3+ in the Portland study was 75%, as opposed to 49% for cytology (PAP2+).[161] A Dutch study produced a figure of 93% as opposed to 64%[126], while the corresponding results for one German study were 97% and 43%.[129]

In a series of nine randomised screening trials, the hrHPV screening test (alone or in combination with cytology) was compared with cytology alone (conventional smear or LBC).[77,128,162-169] The results of the first round of screening are consistent with those obtained by cross-sectional studies. [159] The results of a second round of screening in four screening trials have been published.[25,131,158,170] The Committee addresses the results of these trials here.

The Dutch Population-Based Screening Study Amsterdam (POBASCAM) trial has been running since 1998. This involves the introduction of an hrHPV test into the current screening programme.[77] The combination of hrHPV/ cytology is compared with cytology alone. In the first round of screening, the combination of hrHPV/cytology detected 70% more CIN3+ lesions than cytology alone. This amounted to 7.9 cases per thousand participants versus 4.7.[25] Was this simply a question of overdiagnosis, or were these significant abnormalities? The latter does indeed appear to be the case, as the results of the second round (five years later) provided a contrasting view. Here, 55% *fewer* cases of CIN3+ were detected in the hrHPV/cytology branch of the study than in the control group (cytology alone), amounting to 2.9 per thousand versus 6.3. Accordingly, the total number of women with CIN3+ over the two rounds did not differ between groups. The results for CIN2 were in agreement with this. The authors concluded that the implementation of hrHPV testing in cervical screening leads to earlier detection of CIN3+. Earlier detection of such lesions could permit an extension of the screening interval.[25]

With regard to CIN3+, the second-round results from the Swedescreen trial correspond to those obtained by POBASCAM (Table 3).[158] One difference is that the increased number of CIN2 cases during the first screening round, in the hrHPV-branch of the study, was not fully offset by fewer cases of CIN2 in the second round. This suggests that there had been some overdiagnosis of regressive CIN2 in the first round. This might be due to the relatively aggressive

follow-up after a positive hrHPV test (cytology, followed – twelve months later – by cytology *and* an hrHPV test).

In the British ARTISTIC (A Randomised Trial In Screening To Improve Cytology) trial, hrHPV testing was compared to cytology (LBC) in women aged between 20 and 65 as part of the NHS screening programme.[170] As with POBASCAM and Swedescreen, in the hrHPV branch of the study there were fewer CIN2+ or CIN3+ lesions in the second round than in the first.[170] Interestingly, in the first round, the hrHPV test failed to outperform cytology in terms of the number of CIN3+ cases identified. In addition to the young age of the study group, there are various explanations for the slight difference in performance found here. Firstly, in this trial, LBC may have detected many clinically insignificant abnormalities.[171] What may have tipped the balance in favour of overdiagnosis by LBC is that 13% of first-round smear tests were classified as abnormal (initially this was as much as 17%) and that more than 5% of the participants underwent colposcopy. Moreover, it was very often the case that no action was taken in response to a positive hrHPV-test.[172]

The Italian NTCC (New Technologies for Cervical Cancer Screening) trial involved women aged between 25 and 60.[131] Among women above the age of 35 in the hrHPV branch of the study, more cases of CIN2 or CIN3 were found in the first round (twice as often as with cytology) while fewer cases were found in the second round (half as often).[131] This did not apply to women below the age of 35. The researchers concluded that HPV-based screening is more effective than cytology in detecting persistent high-grade lesions earlier and providing a longer low-risk period. However, in younger women , HPV screening leads to overdiagnosis of regressive CIN2.[131]

Table 3 Relative risk (RR) of CIN3+ in the second screening round in women with a negative hrHPV test in the first screening round. Relationship between hrHPV screening and cytology.[173]

Trial[ref]	Observation period	RR (95%-confidence interval)
POBASCAM[25]	five years	0.43 (0.28-0.66)
Swedescreen[158]	three years	0.53 (0.29-0.96)
NTCC[131]	three years	0.48 (0.21-1.11)
ARTISTIC[176]	three years	0.52 (0.28-0.97)
Total		0.47 (0.35-0.63)

Taken together, the screening trials show that hrHPV screening is 1.3 times more sensitive for CIN2+ than cytology, and 1.2 times more sensitive for CIN3+.[173] In all four trial screening programmes for which the results of the second screening round have been published, CIN3+ was detected earlier by hrHPV screening. A negative hrHPV test in the first round halves the risk of CIN3+ in the second round (Table 3).

The results of a Dutch trial and seven other European trials indicate that the hrHPV test has a high negative predictive value (NPV); over 99% in women above the age of thirty).[126,174] The risk of CIN3+ within a period of five years after a negative hrHPV test is 0.2%, which is considerably less than the risk following negative cytology (0.8%).[25]

HrHPV screening in combination with cytology is barely more sensitive than hrHPV screening alone. [25,170,175] It also has some major drawbacks (see below).

5.3.2 *Specificity*

While HrHPV screening is certainly more sensitive than cytological screening, it is also less specific (Table 4).

An hrHPV test gives a positive result in 4-5% of women between the ages of 30 and 60.[26,77] Before it can become truly attractive as a screening method, hrHPV screening must reduce the risk of CIN3 *and* cancer to a greater extent than cytology. In addition, it must also keep the number of clinically insignificant CIN2 results (and the associated unnecessary colposcopies) to an absolute minimum.[177] Several hrHPV-screening trials showed evidence of an increase in regressive CIN2, resulting in follow-up testing or even treatment.[131,158,170] This increase is in addition to the overdiagnosis that afflicts cytological screening. It is therefore important to limit the amount of overdiagnosis involved.

One way of tackling this is by prudently selecting an appropriate lower age limit for the screening programme's target population. Screening (including hrHPV screening) is clearly not worthwhile in women below the age of thirty.

Table 4 Sensitivity and specificity of hrHPV screening versus cytology. Adjusted for non-response rate at follow-up testing.[26]

	Screening test	Endpoint CIN3+ (95% confidence interval)	Endpoint CIN2+ (95% confidence interval)
Sensitivity	hrHPV cytology	91.9% (61.0-96.7) 64.6% (43.3-73.1)	82.0% (62.9-89.6) 50.5% (38.4-58.0)
Specificity	hrHPV cytology	95.6% (95.3-95.8) 98.7% (98.5-98.8)	96.0% (95.7-96.3) 98.9% (98.7-99.0)

Such individuals often exhibit transient hrHPV infections that do not result in high-grade CIN [178] or regressive CIN2.[179]

Secondly, it would be counterproductive to combine hrHPV testing and cytology as a primary screening method. This is because the combination of hrHPV/cytology is no more sensitive than hrHPV alone.[25,170,175] POBASCAM showed that women whose hrHPV test and cytology were both negative (0.1%) had a five-year risk of CIN3+ that was statistically not significantly lower than the risk for all women with a negative hrHPV test, regardless of the outcome of cytology (0.2%).[25] So not only does the combined use of hrHPV/cytology yield no benefits, it also leads to many unnecessary referrals, [25,128,158,170,175,180] while doubling the screening costs. Accordingly, it has an adverse cost-effectiveness ratio.[181, 182]

Thirdly, it is not appropriate to refer everyone with a positive hrHPV test (4-5% of all participants) for colposcopy. The specificity of the screening method improves considerably if the decision about referral is dependent on the outcome of a second test (triage), *e.g.* cytology.[26,89,175,183] The Committee will revisit this issue in Chapter 7.

5.3.3 *Preventive effect*

The ultimate goal of screening is to prevent cervical cancer, thereby eliminating the associated mortality. The preventive effect of hrHPV screening was first demonstrated in a randomised trial in India (131,746 women between the ages of thirty and sixty, follow-up eight years). The results showed that, compared to a control group (who received standard care), a single offer of an hrHPV test halved women's risk of developing advanced cervical cancer and of dying from this disease.[184] Compared with a control group that was given a single offer of cytology, the risk of cervical cancer after a negative hrHPV test (3.7 per 100,000 woman-years) was found to be significantly smaller than the risk following non-abnormal cytological findings (15.5 per 100,000 woman-years).

HrHPV screening even appears to be effective in countries that already have a long tradition of screening and a lower incidence of cervical cancer. In 2010, the NTCC trial produced convincing evidence that hrHPV screening provides more effective protection against cervical cancer (0 cases in the second round) than cytology (9 cases, p=0.004).[131] The final results of the second round of POBASCAM confirm that hrHPV screening provides more effective protection against cervical cancer than cytology. The former had four cases in the second round and the latter 14, which equates to a relative risk of 0.29 (95%confidence

interval 0.10-0.87).[185] As yet, the other ongoing trials have not published any data concerning this protective effect.

5.3.4 *Duration of preventive effect*

HrHPV screening detects high-grade CIN earlier than cytology. All four randomised screening trials with second-round results indicate that hrHPV screening halves the risk of CIN3+ in the second round (Table 3, page 54). This means that the screening interval (currently five years) can be extended, which will reduce the frequency of screening. Following a negative hrHPV test, how long does the risk of high-grade CIN remain acceptably low?

Results obtained from POBASCAM show that the risk of CIN3+ within a period of five years after a negative hrHPV test is 0.2%, which is considerably lower than the risk following negative cytology (0.8%).[25] This is confirmed by an analysis of data from seven other European studies, in which the corresponding risks are 0.3% and 1.0% for CIN3+ within six years.[174] In women over the age of thirty, the Portland study indicated that the risks of CIN3+ within a period of ten years were 0.5% versus 0.8%.[32] For CIN2+, the HART study gave a risk of 0.6% versus 1.0% within eight years.[186]

The Committee has determined that, after a negative hrHPV test, the risk of CIN3+ remains below the risk level of the current programme's screening interval for at least six to ten years (0.8% five years after negative cytology). It concludes that, if the decision is taken to adopt hrHPV screening, the screening interval can safely be extended to eight to ten years, without increasing the risk of interval cancer.

5.3.5 *Efficiency*

The above details show hrHPV screening to be significantly more sensitive than cytology. The next question is how efficient would hrHPV testing be in the Netherlands, in terms of achieving further reductions in the incidence of cervical cancer? Given that there are limited resources, choices will have to be made about how the available funds should be spent. Cost-effectiveness analyses highlight the health gains (life expectancy, quality of life) and the associated costs and savings.

The Committee was given details of the results of two simulation models for cost-effectiveness analysis. One model was developed by Erasmus MC in Rotterdam, the other [106,108] by the VU University Medical Center in

Amsterdam.[182,187] Erasmus MC uses a population model that simulates the life histories of eight million women born between 1939 and 1992. After 2009, women born before 1939 were too old to participate in the screening programme, while those born later than 1992 have been (or will be) invited to attend for HPV vaccination. The simulated screening programmes start in 2009 and continue until all of the women have passed through the programme. The health effects and costs of hrHPV screening are compared to the current screening programme.

VU University Medical Center uses a cohort model. The analysis monitors cohorts of twenty million women from the ages of ten to one hundred. Health outcomes and costs are only taken into account from the age of thirty onwards.

The Committee adopted Dutch guidelines for a discount rate of 1.5% per year for effects and 4% for costs. Differences in outcomes are largely explained by the type of model used. In the population model, some women do not complete the entire programme, as they were already relatively old when it started. As older women are less likely to acquire hrHPV infections or a high-grade CIN, population models generate lower values for costs and health effects than cohort models. In the following passages, the Committee summarises the most important results generated by these models. It presents its general conclusions and recommendations in Chapter 7.

Maintaining cytology as the primary test

Consider a situation in which the current screening programme is maintained, with cytology as the primary test and the only policy change being the implementation of hrHPV testing as a triage in cases of Pap2/3a1 (BMD) and immediate referral following a positive hrHPV test. This would provide only limited health gains compared to the current policy on mild abnormalities (follow-up smear after six and eighteen months, Table 2). This adjustment does lead to disproportionately more referrals (11% according to the VU University Medical Center model).

Liquid based cytology

Assuming an additional cost of EUR 11.70 per test, the use of LBC as a primary screening method is not a cost-effective alternative in a situation where the number of inadequate smears is already very small.

Introduction of hrHPV testing as the primary test

Modelling shows that use of the hrHPV test as a primary screening method can generate significant health gains. This even applies if the cost of this screening programme (in the financial and economic sense, including triage, and assuming a cost of EUR 33 per hrHPV test) remains approximately equal to the cost of the current screening programme.

Follow-up testing after a positive hrHPV test as the primary test

Modelling has been used to explore triage/follow-up strategies for hrHPV-positive women. The end-point was cumulative risk of CIN3+. The tests involved were cytology, hrHPV, HPV16/18 genotypng, and HPV16/18/31/45 genotyping. Cytological triage was based on co-collection at t=0 (co-collecting a glass slide specimen, which is only stained and evaluated in response to a positive hrHPV test). Triage with cytology at t=0 and hrHPV at t=6 months leads to many unnecessary referrals[26], as hrHPV is less specific than cytology for high grade CIN. The purpose of triage is not to establish that the infection has been cleared, but to rule out the possibility that infection has resulted in abnormalities.

Number of screening rounds, screening interval

As hrHPV screening detects CIN3 lesions and cervical cancer earlier, the present frequency of screening can be reduced. The optimal screening strategy amounts to five or six rounds of screening throughout a woman's life, instead of seven. The five-round strategy is 5-12% more effective than the current screening programme, while the costs remain about the same. The second strategy (involving six screening rounds), is even more effective, but the associated costs are higher than those of the current screening programme.

In the current programme, women are invited for screening once every five years. The modellers have examined the question of whether hrHPV screening too should ideally involve a fixed screening interval (*e.g.* eight years). An age-dependent interval proved to be more cost effective. This could involve extending the intervals as individuals age, *e.g.* screening at the ages of 30, 35, 40, 50 and 60.

A separate screening programme for women aged thirty?

The results generated by the Amsterdam and Rotterdam models differ on the issue of whether women aged thirty should be tested for hrHPV, or whether better results can be obtained by using cytology as the primary screening test for women of this age. The Amsterdam model's results show that significantly greater health benefits (in terms of preventing cervical cancer and the associated mortality) can be obtained if hrHPV screening is extended to include 30-year-old women.

The Rotterdam model gives a slight preference to cytology at the age of thirty. Calculations performed using the Rotterdam model show that while cytology at the age of thirty does have cost benefits, there are no advantages in terms of extra years of life gained, whether or not these are adjusted for quality of life.

5.3.6 Which hrHPV test?

The hc2[27,128,131,155,161,170,184,186,188-191] and the GP5+/6+-PCR enzyme immunoassay[25,41,183,192] are the only hrHPV tests that have been used in large cohort studies and in the randomised trials which showed that non-regressive CIN can be detected earlier this way than with cytology. These tests have a high degree of inter-laboratory and intra-laboratory reproducibility.[193-195] Accordingly, the Committee considers these tests to be both clinically valid and reliable.

It is important to distinguish between a test's analytical validity and its clinical validity. Analytical validity refers to the detection or exclusion of an hrHPV infection, including transient infections that are clinically irrelevant. The second aspect (clinical validity) concerns clinically relevant hrHPV infections that have led (or will lead) to CIN2+. The purpose of screening is not to detect every single hrHPV infection, but to reveal relevant abnormalities (high-grade CIN or worse).

There are about thirty commercial tests for hrHPV. These differ considerably in terms of clinical sensitivity and specificity. For instance, the SPF10-PCR test has greater analytical sensitivity than GP5+/6+-PCR, but their clinical sensitivity is the same, and the former has a lower clinical specificity. If this test is used for screening, it produces many more false positives without providing any greater protection against cervical cancer.[196] The same applies to Cervista, which was recently approved by the FDA. This test produces positive results two to four times more often than hc2, but it has a much lower clinical specificity.[197]

Such tests are not suitable for screening. It is therefore important to have guidelines that hrHPV tests must meet before they can be used for this purpose. In June 2010, the Dutch Society for Pathology's (NVVP) Molecular Diagnostics in Pathology working group drew up detailed guidelines (www.pathology.nl), based on those produced by an international consortium.[198,199] These include the minimum requirements that a laboratory must meet to ensure that the quality of the hrHPV test can always be guaranteed. These guidelines can be used to approve candidate tests for screening (provided that they are reliable and have been properly validated) without the need to conduct large-scale longitudinal studies.

The following requirements have been formulated (www.pathology.nl):

- a sensitivity for CIN2+ in women aged thirty or above that is no less than 90% of the clinical sensitivity of the hc2 (as demonstrated by non-inferiority score testing).[200] This guarantees that the HPV test will have a high negative predictive value (NPV), making it possible to extend the screening interval for hrHPV-negative women
- a specificity for CIN2+ in women aged thirty or above that is no less than 98% of the clinical specificity of hc2 (as demonstrated by a non-inferiority score test).[200] This threshold value was chosen to limit the number of false positive test results
- intra-laboratory reproducibility and inter-laboratory agreement of at least 87%. This ensures that day-to-day testing will be conducted robustly and highly reliably.

The Committee attaches great importance to compliance with the guidelines, as this guarantees a high degree of clinical sensitivity while also reducing the risk of false positive screening results to a minimum.

HrHPV tests that do not focus on the detection of DNA (*e.g.* those targeting mRNA) do not comply with the guidelines as their NPV is not known, which means that the optimal screening interval is also unknown. In such cases, large-scale longitudinal studies are needed.

5.4 Conclusion

The Committee concludes that there is clear evidence that hrHPV screening is more effective than cytology as a primary screening method. As hrHPV screening detects high-grade CIN and cervical cancer earlier, the present frequency of screening can be reduced. Testing with a clinically validated,

reliable hrHPV test is significantly more sensitive, but less specific for CIN2+. A suitable triage test should compensate for this.

In the medium term, the Committee does not anticipate the arrival of any new testing methods that are scientifically sound enough to provide a viable alternative to an hrHPV screening programme.

While liquid-based cytology reduces the number of inadequate smears, its test performance is no better than that of the conventional smear test, and it is also more expensive. Its lower specificity means that more women will be required to undergo unnecessary follow-up tests. LBC is already being widely used in the Netherlands for primary screening. The Committee feels that this is scientifically unfounded.

LBC makes it possible to partially automate the screening process. However, experimental studies have found that computer-assisted screening is less sensitive than manual screening and, despite the increased productivity involved, no more cost effective.

Chapter 6

Measures to boost participation

By far the most important prerequisite for an effective screening programme is an ability to reach the target group. However, behavioural research has produced relatively little "hard" data on this topic. Published research shows that – in half of all cases – the incidence of cervical cancer is related to non-participation in screening or follow-up tests, even where a screening programme has been operating for many years.[118,119,201-205] Accordingly, the highest priority is given to measures aimed at reaching those subgroups that are less inclined to participate and which, as a result, are at greater risk of developing cervical cancer.[119]

When considering such measures, it is important not to lose sight of the fact that individuals are free to decide whether or not they want to participate in screening. People's personal responsibility must not be compromised in any way. It is up to the individual to decide whether the benefits of participating in screening outweigh the drawbacks. One essential element of this freedom of choice is that potential participants must be well informed, another is that the choice of whether or not to participate should be in line with their general attitude towards screening. The concept of informed choice[63] is the principle on which the provision of information on cervical cancer screening in the Netherlands is based.

6.1 Determinants of screening uptake

There is a clear link between women's socio-demographic characteristics and their participation in screening. Uptake is lower than average among younger women, women from ethnic minorities, women in urban areas, or those with a low socio-economic status.[54,61,67,206-209]

It is a recognised fact that studies of people's reasons for not participating in screening are difficult, due to the high non-response rate among non-participants. This is often due to medical reasons. Beyond that, the barriers are mainly practical in nature, i.e. being unable to make a suitable appointment, and having a poor command of the Dutch language. In addition, there are emotional barriers, such as embarrassment, anxiety, previous adverse experiences, and dissatisfaction with the GP.[208, 210-212]

The requirement for participants to pay a personal contribution is a major barrier.[213] In 2003, when women in Stockholm were required to pay EUR 14 per smear, participation dropped by 23%. However, participation returned to its original level following the withdrawal of this measure in 2005.[57]

Both participants and non-participants have a relatively poor understanding of cervical cancer, and of the pros and cons of screening.[211,214] A low level of participation is linked to various misunderstandings. One of these is the assumption that cervical cancer is a disease of older women, another is the commonly held notion among ethnic minority groups that if you don't have any symptoms then you don't need a smear test.[212] Many people do not participate in screening programmes because they are not convinced that this has anything to offer them. They give reasons such as "There's nothing wrong with me", "I have a healthy lifestyle", "I do my own health checks", "I am not sexually active (or am no longer sexually active)", "I visit my GP on a regular basis, so there is nothing to worry about, is there?"[212]

6.2 Measures to boost participation rates

6.2.1 Invitation strategy

Studies have shown that participation is mainly influenced by the invitation strategy adopted.[215] In the case of invitations issued by screening organisations, the women in question have to contact their GP themselves to make an appointment to have a smear taken. Having to take the initiative to undergo what is often perceived as being an unpleasant test creates an extra barrier.[211, 216,217]

The adoption of a systematic call scheme based on invitation letters signed by GPs can eliminate this extra barrier by suggesting an appointment at a specific date and time. A nationwide survey found that participation increased when a general practice was involved in the invitation system.[218] However, GPs are only involved in this process in half of all cases.

Other measures to remove barriers to participation involve setting up a walk-in surgery and the option of having a smear taken outside office hours.[217] However, the effects of such measures have not been studied.

Invitations issued by people's own GP leads to greater participation than invitations from a screening organisation.[218-224] This difference can become even more marked if GPs themselves send reminders to those women who failed to respond to the initial invitation.[219, 220]

Are more women really participating, or could this simply be an artefact produced by different ways of defining participation? After all, GPs are better able than screening organisations to correct their participation figures for women who, for medical reasons, are not eligible for a smear (pregnancy, being treated by a gynaecologist, hysterectomy). Given the sheer number of women who have undergone hysterectomy (over 100,000),[225] a substantial bias might easily develop.

In this case, however, clearly defined participation figures were used, thereby eliminating the possibility of bias.[218,220,221,223,226] In a 3-year nationwide study, GPs had a 15% (percentage point) higher gross participation and a 20% higher net participation.[218] Subsequent studies showed a 10-15% greater gross participation.[221,223] It was found that when GPs were only involved in repeat invitations, gross participation was 10% higher and net participation 15% higher than when the invitations and reminders were issued by screening organisations.[218]

A randomised study in Italy found that GPs achieve much higher participation figures than screening organisations.[216]

The effect of an invitation from the GP on participation figures is greater than average in subgroups where there is restricted participation, such as younger women, those with a lower socio-economic status, or women from more urban areas.[219,223] This is even more applicable to non-Western women.[223]

Leaving the issuing of invitation letters to GPs does have certain practical drawbacks. For instance, this makes it difficult to ensure that they all provide the latest information set to women in this target group. Moreover, there are many different GP information systems, which makes it difficult to implement policy adjustments. Also, the relevant data for women who do not need to participate (or who no longer need to do so) are not always passed on to the screening

organisations. The Committee recommends that this be incorporated into the implementation study (7.7).

6.2.2 *Invitation methods used by GPs*

There is a substantial variation in participation, even when GPs issue the invitations. Uptake can range from 60% to 87% within a single region.[217] Further research involving telephone interviews and focus group meetings has shown that this difference mainly depends on the extent to which the invitation is noncommittal.[217] Letters of invitation containing a fixed, preallocated appointment time produce greater participation than open invitations that require women to make their own appointment.[213,216,217,227,228] This is entirely in line with expectation, given that invitations from screening organisations (with open appointments) result in lower participation. In one Italian trial, GPs who issued invitations containing a preallocated appointment achieved a 13%-point greater participation figure than those who sent an open invitation.[216] The situation in Italy is certainly different from that in the Netherlands, nevertheless the trial in question was randomized. European guidelines strongly recommend the use of fixed appointments.[58]

Is the use of a fixed appointment in keeping with the principle of self-determination? The Committee thinks that it is, provided it is made clear that participation in screening is not mandatory. Partly for practical reasons (women working away from home, menstrual cycle), it is important that this appointment can easily be changed (email, website, phone).

The timing of a reminder seems to be important. It would be beneficial if these reminders were issued sooner (after about six weeks instead of after six months).[59] This much is clear, because such a long interval tends to undermine the message that participating in screening is important. However, this aspect has not been well studied.

One trial investigated the effect of a second reminder. Women were selected at random from those who had not responded to invitations in 2005 or 2006 (nor to a reminder after six months) to attend the screening programme in the Dutch provinces of Noord-Holland and Flevoland. This PROHTECT (protecting by offering HPV testing on cervicovaginal specimens trial) trial control group received a new invitation to have a smear taken. Twelve percent of these non-attendees visited their GPs to have a smear taken.[114,229]

6.2.3 *Other initiatives*

A publicity campaign had little effect.[230,231] Even personalised letters of invitation containing information tailored to each individual's risk profile failed to improve the participation rate, and may even have been counterproductive.[232,233] One study in the Netherlands investigated the effect of circulating an informative magazine to thirty-year-old women two weeks before they received the actual invitation. The magazine was found to have a beneficial effect on people's attitudes, knowledge, and intention to participate, but not on actual participation.[234]

Women who participate in screening programmes irregularly, or not at all, are particularly difficult to reach.[233] A randomised trial among women who had not had a smear test for fifteen years tried a range of different approaches, but none of these achieved more than 5% participation.[231]

6.3 Self-sampling

One potential new method for boosting participation involves a screening test in which the subjects collect their own sample, at home. The requisite collection material (brushes, lavage devices, swabs, tampons) can be sent to them by mail, and posted back to the laboratory after use.

6.3.1 *Test characteristics*

Self-collected samples are not suited for accurate cytological assessment. This is because half of the CIN2+ lesions that can be detected using conventional smears would be missed.[235,236] The reason is that self-collected samples contain few intact epithelial cells from the "transition zone", where the external orifice of the uterus meets the cervix, which is where cervical cancer usually occurs. During pelvic examinations, smears can be taken directly from the cervix via a duck's-bill speculum.

However, good results can be obtained with hrHPV tests on self-collected material. This is because the virus spreads from the cervix into the vagina, and intact cervical cells are not needed to demonstrate the presence of the virus.

Analytical validity

A meta-analysis found good agreement between self-sampling and physician-sampling for hrHPV detection. [237] This is confirmed by results obtained from other studies.[236,238-241] In various other studies, however, the self-test appeared to be less sensitive.[235,242] This is probably due to the nature of the collection device (cotton swab instead of a brush or lavage device).

Occasionally, a higher hrHPV detection rate was found in self-collected vaginal samples than in physician-collected (cervical) samples.[114,243-245] This is probably due to restricted cross-reactivity of the hybrid capture 2 test (hc2) to low-risk HPV types, which are slightly more common in the vaginal epithelium.[246] Self-tests also detect vaginal infections. Finally, some infections may clear in the interval between the self-test and the physician-collected sample.[229]

Clinical validity

HrHPV testing of self-samples appeared to be at least as sensitive as cytology for CIN2+ on physician-collected samples, though often less specific.[235,236,238,247-252] Furthermore, studies where self-test methods involving a brush or lavage were used often exhibit greater sensitivity for CIN2+[236,249, 250,253] than studies which a Dacron or cotton swab was used.[238,247,248,251,252]

No randomised studies with CIN2+ as an endpoint have been carried out to compare performance of hrHPV detection in self- versus physician-collected samples. While observational studies (many with a cross-sectional design) have been carried out, few of them were large enough for statistical analysis. Two of them indicate that self-tests are less sensitive[242, 251], while four show that self-tests are just as sensitive as an hrHPV test on physician-collected samples.[236, 238,254,255]

Acceptance

The initial studies into the acceptance of a self-test involved patients who had been referred to a gynaecologist (for colposcopy). While the results of studies in selected study populations of this kind (gynaecological patients in a treatment situation) cannot be directly extrapolated to the target population, they can provide useful indications.

These indications are mostly favourable. Self-sampling might enable women of diverse origins to sidestep any cultural or religious objections.[256] In selected study populations of this kind, virtually every woman who is offered a self-test

actually makes use of it.[240,245,257] Very few women either have difficulty using a self-test or submit a sample that is not of sufficiently good quality to permit assessment.[114,238,258] When asked about their experiences, those using self-testing generally preferred this system to an internal examination with a duckbill speculum.[238,239,258] A self-test can avoid the drawbacks that women sometimes associate with screening programmes, such as discomfort or feelings of shame when a smear is being taken, or logistical problems when making an appointment.[215,235,244,257,259-261]

Some other studies indicate that many women prefer the conventional smear, not because they object to self-sampling, but because they are unsure about how to do it properly and do not trust the result.[235,256,257,261,262] Nothing is known about the extent to which such uncertainty is due to the type of self-test used and to the information provided about how to perform the test.

Research results in the context of screening programmes

Research on self-sampling in the context of screening programmes is almost entirely restricted to non-attendees (non-participants in regular screening). In 2006 PROHTECT, a randomised study of self-sampling, was launched in the Dutch region of Amstelland/Meerlanden. It was linked to the screening programme. In a previous pilot study, 2546 non-attendees were sent a self-sampling test kit. Of this group, 34% completed the test.[263]

These results were confirmed in PROHTECT1 (using a lavage device),[114] and in PROHTECT2 (Viba-brush).[229] PROHTECT involves a total of 54,482 women who had not participated in the screening programme for at least six years. PROHTECT1 and PROHTECT2 produced broadly comparable results, and a meta-analysis of their outcomes revealed that almost 30% of the non-attendees used the self-test.[264] It was also found that indigenous non- attendees participated more often (32%) than non-Western ethnic minority non-responders (22%), and that women who had never been screened before participated more frequently than those who participated irregularly. In the control group of 545 non- attendees, the intervention consisted of an additional reminder prior to a conventional smear at the GP's surgery. The participation rate was 12%.

Nine percent of non-attendees who did the self-test had a positive hrHPV test. These individuals were referred to their GP for cytology.[264] This second test is used for triage, to better predict which women will have CIN2+. Nearly 90% of those women who were referred actually visited their GP. The smear was abnormal in 30% of these cases (PAP2+). Ninety five percent of this group

followed the advice that they were given, which was that they should immediately consult a gynaecologist for further diagnosis (colposcopy).

HrHPV-positive women whose smear showed no cytological abnormalities or who did not take a smear test were advised to visit their GP after a period of 12 months for a follow-up consisting of cytology and hrHPV testing. Only 58% of those in this group acted on the advice. Women whose smear or hrHPV test (or both) were positive were referred for colposcopy, but only 55% acted on this advice.

Ultimately, CIN2+ was detected in 1.4% of the 15,228 women who took the self-test (13 women were found to have cervical cancer, while another 205 women had CIN2 or CIN3). This yield is higher than among those participating in the current screening programme. In the first round of POBASCAM, 0.7% of the control group (cytology) were found to have CIN2+, while the corresponding figure for the intervention group was 1.1%.[25] The yield delivered by self-sampling was greatest among women who had never before been screened (excluding 30-year-old women).

In a Swedish study, 2829 of non-attendees who had not attended an organised screening for at least six years were sent application forms for self-sampling. Three weeks later, they were sent a reminder to apply for the self-test.[250] After two months, those women who had requested the test were sent a reminder about actually completing the self-test. Nearly 40% of the total number of non-attendees (1107/2829) accepted home sampling. In this group, the yield (2.0% CIN2+) was twice as large as in the regular screening programme (0.9%). Two other studies succeeded in getting 30% of non-attendees to actually take a self-test.[115, 265]

6.3.2 Remaining questions

In terms of participation and yield, self-sampling achieved good results. However, there may well be scope for further improvement. Seventy percent of those non-attendees who were offered a self-test did not participate. Furthermore, a significant proportion of those who did accept home sampling and who were found to be hrHPV-positive (one quarter of whom have CIN2+)[114] discontinued their participation at some stage. Could the follow-up procedure be simplified? One way of improving the yield of self-sampling still further would be to reduce the number of women who terminate their participation. With so much at stake, attempts should therefore be made to reduce the number of steps in the follow-up procedure. For instance, following a positive hrHPV test, the self-collected

sample could be immediately used for a molecular test.[266] This option will be explored in a subsequent PROHTECT trial.[70]

One possible drawback of using self-sampling for non-respondents is that those women who do intend to attend the organised screening might not respond to their invitation in the hope of obtaining a self-sampling device. This could actually undermine the health gains and efficiency of the screening programme. Accordingly, the introduction of any such "safety net plan" should be carefully implemented and properly evaluated.

Ultimately, it is a matter of whether the entire target group should be given the option of self-sampling, in addition to having a smear taken at their GP's surgery. The Committee anticipates that a great many women will prefer self-sampling, but this aspect has only been investigated in a small Indian study. This study showed that self-sampling increased participation from 54% to 72%.[240] The yield, too, was significantly greater than with the conventional smear test (for cytology). However, a number of questions remain to be answered.

For instance, some studies have shown that self-collected samples produce hrHPV-positive results (and false-positive results) more often than physician-collected samples.[114,245] This matter needs to be explored in greater detail.

There is also uncertainty surrounding participation. It is not a foregone conclusion that more choice will result in greater participation. For instance, experimental colorectal cancer screening in France, Italy and Australia showed that offering a choice of different screening methods failed to increase participation.[267-270]

A third point concerns triage. Unlike women who take an hrHPV test at their GP's surgery, those whose self-test produces a positive result then also have to visit their GP for triage. That extra step involves about 5% of regular participants (and 9% of the non-attendees). This means that 95% of self-testing women do not need to visit their GP, which also represents a significant financial benefit.

6.4 Conclusion

The Committee has determined that in only half of all cases are GPs involved in inviting women to attend for screening. It concludes that significant increases in participation could be achieved if more GPs could be persuaded to issue such invitations themselves. This is because the effect of an invitation from a woman's own GP has the greatest effect in subgroups where there is restricted participation, such as younger women, those with a lower socio-economic status,

or women from more urban areas. This is even more applicable to non-Western women.

The Committee recommends that a specific date and time for attendance should be included in the letter of invitation. However, that letter should offer ample scope for women to change their appointment, where necessary.

As an alternative to invitations being issued by a woman's own GP, screening organisations can issue the first invitation, and the GP can issue any reminders. In such cases, participation is 5% points lower than when the initial invitation is also issued by the GP.

The Committee recommends that those who do not respond to the initial invitation should be sent written reminders after about six weeks, rather than waiting for six months.

One way to significantly reduce non-response might be to offer self-sampling to non-responders after a period of three to six months, for example. The introduction of any such "safety net plan" should be carefully implemented and properly evaluated.

It is too soon to offer the option of self-sampling directly to all women, as an alternative to a smear (for an hrHPV test) taken at their GP's surgery. The Committee recommends that this approach should be studied experimentally, in a trial region.

By far the most important prerequisite for an effective screening programme is an ability to reach the target population. The Committee recommends that this issue should be the subject of further behavioural research.

Chapter 7

Conclusions and recommendations

This final chapter sets out the Committee's recommendations concerning the design and mode of implementation of the new-style screening programme.

7.1 Provision of information

The effective provision of information is a crucial aspect of the switch to hrHPV screening. People have a poor understanding of cervical cancer, and of the pros and cons of screening. Until recently, most women were entirely unaware of HPV.[271] It seems that, with the advent of HPV vaccines, this is about to change.[272] Information about HPV and its causal relationship to cervical cancer is now widely available (www.bevolkingsonderzoeknaarbaarmoederhalskanker.nl).

Participating in screening gives rise to anxiety and uncertainty, especially for those with abnormal test results. This aspect has been mainly studied among the participants in cytological screening. Even a slightly abnormal smear (Pap2/3a1, BMD) can cause significant stress for the subject in question, at least in the short term.[273] According to one Dutch study, the effect of this is still measurable six months to two years later.[134] Further research (in the form of longitudinal studies) is needed.

What effect does hrHPV screening have in this regard? Firstly, the introduction of hrHPV screening could reduce participation. Prior to POBASCAM,

those women who were eligible to participate in the screening programme were sent a written questionnaire and a leaflet containing information about hrHPV. However, it seemed that acceptance of hrHPV as the primary screening method would not be a problem.[274] In practice, participation in the hrHPV branch of the study was no lower than in the standard screening programme. If anything, it was slightly higher.[275] This was also seen in the Finnish trial.[299]

Secondly, hrHPV screening could be even more stressful.[273] The notion that this is a sexually transmitted infection might result in stigmatisation. People might be shocked at the idea of a link (however, remote) between sex and cancer, and this could affect their psychosexual functioning. While there are no data for the Dutch situation, the British ARTISTIC trial did provide an opportunity to properly compare the psychological and psychosexual effects of hrHPV screening and cytological screening.[276] This trial was linked to the ongoing screening programme in the UK.[176] The experimental group received both hrHPV screening and cytological screening. They were also informed of the results. The control group also underwent both tests but, like their GP, they were not informed about the outcome of their hrHPV test. This comparison, which was based on randomisation between women with the same hrHPV status, showed that hrHPV screening did not impose an additional burden, in psychosocial terms.[276]

The GP plays a strategic part in the provision of health information. Accordingly, if the public is to be adequately informed, it is important to provide GPs with up-to-date information on cervical cancer and hrHPV screening. In this connection, the Dutch College of General Practitioners (NHG) standard "*Preventie en vroegdiagnostiek van cervixcarcinoom*" (Prevention and early diagnosis of cervical cancer)[69] needs to be updated.

The Committee recommends that the NHG standard be updated, and that use be made of experience gained in the course of hrHPV screening in screening trials and with the associated materials.

7.2 Screening strategy

7.2.1 HrHPV testing as the primary screening test

The Committee recommends a switch to hrHPV screening. The continued use of cytology as a primary screening test, alongside hrHPV testing, is not efficient. The Committee has determined that hrHPV screening is significantly more

sensitive than cytology (Table 4). This also includes the precursors of adenocarcinoma, which is difficult to detect using cytological screening. Following a negative hrHPV test, the risk of high-grade CIN and cervical cancer remains low for many years. It is significantly lower than the risk involved following a negative cytology result. HrHPV screening makes it possible to detect virtually every case of high-grade CIN, albeit with significantly lower specificity than cytological screening. A second test (for triage purposes) should compensate, as far as possible, for the disadvantages of lower specificity (false positive screening results, overdiagnosis, overtreatment).

One practical benefit of the hrHPV test versus cytology is that it is objective, another is that it can be automated. Cytology is a subjective test that occasionally produces widely varying results,[277] especially between different countries.[76]

7.2.2 *Triage*

If all those with a positive hrHPV test (4-5% of all participants [26,77]) were to be referred to a gynaecologist for colposcopy, a great many women would be burdened with additional procedures that deliver few benefits. To reduce the number of unnecessary referrals, a positive hrHPV test should be followed by a second (triage) test to better predict which of these subjects will have CIN2+. Referral will only then take place if the triage test, too, is positive. If the triage test is negative, then a management recommendation for a repeat smear test at a later date is sufficient (Figure 2, page 76).

What requirements must a triage test meet? Firstly, the screening must maintain a high level of sensitivity, as you want as few cases of disease as possible to slip through the net. Secondly, the triage test must have high specificity, to restrict any false positive results to an absolute minimum. Thirdly, the number of occasions on which women are recalled for testing should be kept to a bare minimum. Each additional test involves a drop-out rate of around 20%.[25] A high drop-out rate can negate many of the benefits of hrHPV screening, as the ARTISTIC trial demonstrated.[170] Also, the longer the period of uncertainty, the greater the burden on the woman in question.[278] Quicker care is often better care.[279]

The literature suggests a variety of different triage strategies.[26,89,163,181,183,266] This usually involves cytology. Consideration is also being given to options such as genotyping. HPV16 and HPV18 are jointly responsible for 70% of squamous cell carcinomas, and 85% of adenocarcinomas.[35,157,280] In addition, the risk of CIN3 or cancer has been found to be highly genotype-dependent.[32,281-283] The

10-year risk of CIN3+ in the Portland-study was 15% for HPV18 and 20% for HPV16, compared to just 2% for other high-risk types.[32]

Based on the results of VUSA screen (a screening trial in the Dutch Province of Utrecht), a decision tree analysis of fifteen different triage strategies was carried out.[180] The top two were pure cytology, and cytology plus HPV16/18 genotyping. Both triage strategies combine high sensitivity (an NPV of at least 98% for CIN3+ within two years) with high specificity (PPV of at least 20%). Furthermore, women with a positive hrHPV test had to return just once for testing (cytology after six months).

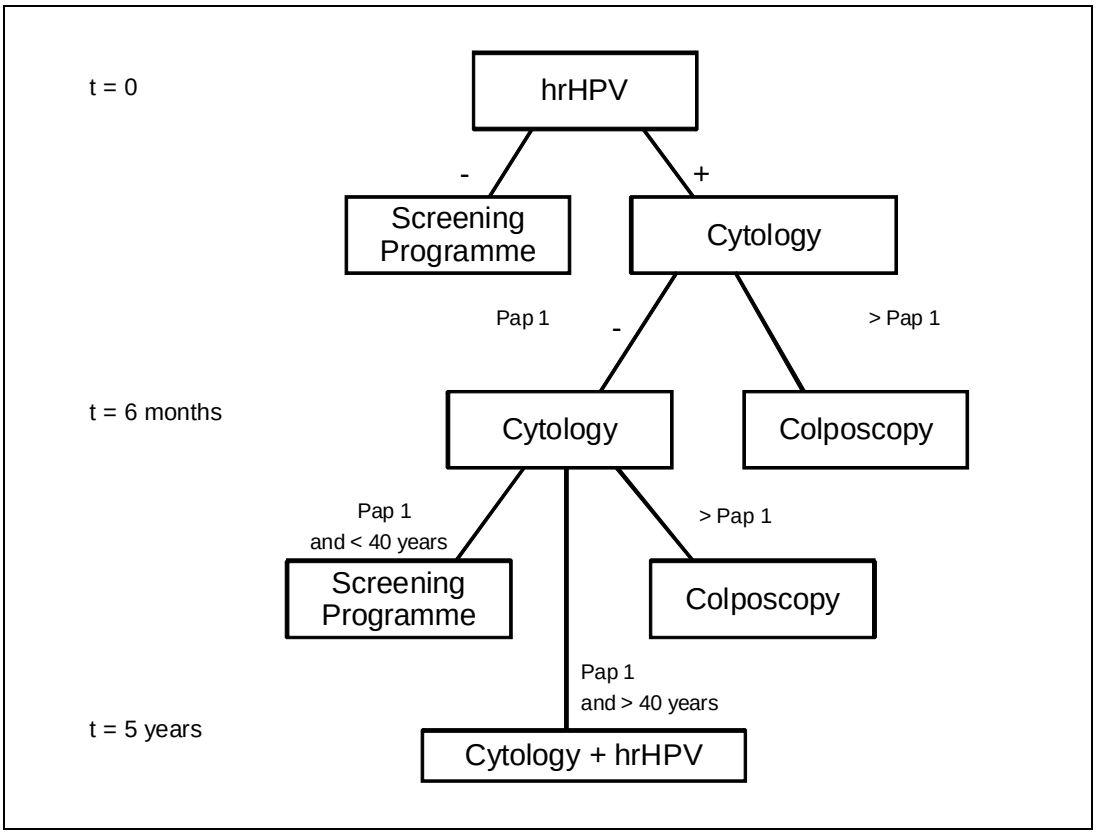


Figure 2 HrHPV screening with cytology triage.

The Committee recommends triage by cytology alone (Figure 2). This can be organised in such a way that women are not required to return immediately after a positive hrHPV test. One way of achieving this is by co-collection, a method that has been widely used in various screening trials. [25,26,284] First a sample is taken, this is then used to make a conventional smear, and finally the brush bearing the remaining material is used for an hrHPV test. Another approach is to use the collection and transport medium associated with the LBC technique. In the event of a positive hrHPV test, the same sample is used for cytological testing.

The Committee advises against the addition of genotyping to cytology at baseline. This makes the logistics of triage more complex, and does not eliminate the need for a follow-up step after six months. The reason for this is that hrHPV-positive women with negative results both from cytology and genotyping have a residual 2-year CIN3+ risk of 2.9%. The corresponding risk is just 0.7% for hrHPV-positive women with negative cytology at baseline and at repeat testing. In the second place, triage plus genotyping leads to more unnecessary referrals for colposcopy than is the case with triage plus cytology alone.[26]

Women with a positive hrHPV test and a negative cytology triage test need a follow-up cytology test after six months. This is because they are still at too great a risk for them to be referred back to the screening programme schedule.[32,285] POBASCAM and VUSA-screen had a 5-year CIN3+ risk of about 5%.[25,26,126] This risk is significantly greater than the generally accepted 5-year CIN3+ risk of 0.8% after negative cytology in the current screening programme.[25]

Why no follow up with hrHPV after six months? As it does not meet the requirement for high specificity, this approach results in many unnecessary referrals, which leaves women in limbo for longer.[26]

7.2.3 Which hrHPV test?

With hrHPV screening, the choice of test is crucial. There are about thirty different commercial tests for hrHPV. These differ considerably in terms of clinical sensitivity and specificity. What requirements must be met by hrHPV testing for screening purposes? In June 2010, the Dutch Society of Pathology's (NVVP) Molecular Diagnostics in Pathology working group drew up detailed guidelines (www.pathology.nl, see also 5.3.5). The Committee attaches great importance to compliance with these guidelines, as this guarantees a high degree of clinical sensitivity while also reducing the risk of false positive screening results to a minimum.

When considering a replacement for hc2 or GP5+/6+-PCR, the main issues are the validity and reliability of candidate screening methods. Such a crucial change in the context of the Population Screening Act would require applications for permits to be submitted (or re-submitted) to the Minister of Health, Welfare and Sport, accompanied by details of the findings of studies into the validity and reliability of the test in question.

7.2.4 *Number of screening rounds, screening interval*

Cervical cancer screening is less cost effective than screening for other, more common, types of cancer.[103,104] However, a switch to the hrHPV test could produce significant improvements in cost effectiveness (Table 5).

The Committee concludes that a five-round screening programme would deliver greater health gains than the current screening programme, without increasing the financial and economic costs involved. Another conceivable scenario would deliver unchanged health gains but at a lower cost. This programme involves cytology for women aged thirty, and hrHPV in the following four screening rounds. That would involve savings of two and a half million euros in screening costs, compared to the current screening programme. In Section 7.2.6, the Committee gives its reasons for not recommending this scenario.

The screening costs might even be lower than is currently assumed in the model calculations. This could compensate for the additional cost of offering self-sampling to non-attendees, which was not included in the model calculations. This is because screening costs are largely dependent on laboratory costs, and the cost per test in the Netherlands has yet to be determined. The model calculations are based on a unit cost of EUR 33. The Committee believes that the cost per test will not exceed this level. In a large laboratory in Sweden, the cost was calculated at EUR 20 per test (personal communication, Dr J. Dillner).

Table 5 Cost-effectiveness of cervical cancer screening compared to no screening. Euros per year of life gained, adjusted for quality of life.

Screening programme	Simulation model			
	Erasmus MC[a]	VUmc[a]	Erasmus MC[b]	VUmc[b]
7 rounds cytology, current programme	5,900		11,300	
6 rounds hrHPV	5,400	6,500	10,200	11,000
5 rounds hrHPV	4,600	4,100	8,700	5,100

[a] 4% discount rate for costs and 1.5% for effects.
[b] 3% discount rate for costs and for effects.

Assuming that 350,000 to 400,000 tests are carried out each year, the centralisation of laboratory testing could substantially reduce screening costs.

Based on the model calculations, the Committee recommends that women be screened on five occasions throughout their life, in the years that they turn 30, 35, 40, 50 or 60 (Table 5). This scheme is not only the most cost effective, it also has the advantage that women will be subjected to two fewer rounds of screening. If there is a switch to a longer screening interval in later life, the Committee recommends that women aged 40, 50 and 60 who had a positive hrHPV test during screening and a negative cytology during triage should be offered an additional screening round five years later. The purpose is to determine whether these hrHPV-positive women have cleared the virus.

Table 6 summarizes the estimated effects of the current screening programme (a minimum estimate, see Section 4.2), and the additional health gains associated with the proposed new system.

7.2.5 Age limits

As indicated in the previous Section, the Committee recommends that the current age limits for the screening programme's target group be retained. Recognising that age limits are often a matter for debate, the Committee explores the arguments in greater depth here.

Lower limit

In the Netherlands, women become eligible to participate in the screening programme at the age of thirty. This is later than in most other countries. From time to time it is suggested that this age limit be lowered. [286,287] On occasion, this issue has even been debated in the Lower House of the Dutch parliament. However, the Committee does not concur with the arguments that have been put forward.

For example, it is claimed that girls now become sexually active at a younger age, resulting in an increasing number of cases of cervical cancer in women under the age of thirty.[287] In the Netherlands, the incidence of cervical cancer among young women, and the associated mortality, are still very low.[7288] Approximately 96% of new cases and 99% of deaths from cervical cancer occur in women over the age of thirty. Incidence peaks between the ages of 35 and 45 (www.ikcnet.nl).

In the 25-29 age group, however, there has been no increase in incidence and mortality. The number of new cases is hovering around twenty per year, after adjustment for cases of cervical cancer detected by screening (the first invitation for screening is issued in the year that a woman turns thirty, so she can still be 29 at the time). The number of women dying from cervical cancer has been fluctuating between zero and four per annum for many years (0.55 per 100,000).[288] Opportunistic screening cannot account for the fact that there has been no increase in incidence and mortality, as women under thirty years of age make little use of this facility.[107]

The second argument put forward in support of a lower entry age suggests a rise in the incidence of cervical cancer in the 30-44 age group. It is claimed that the detection of cervical cancer precursors prior to an individual's thirtieth birthday could counteract that increase. There was indeed a slight increase from 2003 to 2007 (in the 30-39 age group, at least), however this follows – and offsets – a steeper reduction between 2000 and 2003. These fluctuations are attributed to a restructuring of the screening programme in 1996.[7]

In terms of prevented cases of cervical cancer, the number of extra years of life to be gained is substantial. However, the damage that can result from screening is also an important consideration. How do the potential benefits weigh up against the drawbacks?

Fifty-five percent of 30-year-old women participate in the screening programme. If we project this participation figure onto the nearly 100,000-strong population of 25-year-old women in the Netherlands, a reduction in the entry age would boost the number of women taking a smear test by 55,000. In 2008, 8% of 30-year-old women had an abnormal smear. Of these, 1.7% were given an immediate referral for colposcopy. This would equate to 4400 cases with abnormal smears, and 935 direct referrals to a gynaecologist for colposcopy. Assuming that cytological screening in women of this age has a sensitivity of 50%, and that there are almost twenty new cases of cervical cancer in the 25-29 age group, then this would involve no more than five preventable cases

Table 6 Effect of screening programme on cervical cancer incidence and mortality in the Netherlands. Absolute numbers per year.

	Incidence	Mortality
Annual cervical cancer incidence and mortality[a]	707	221
Effect of current screening programme[99]	-330	-175
Additional impact of proposed new structure (VU University model)	-75	-18

[a] Averaged over the period from 2006 to 2009 (http://nkr.ikcnet.nl).

(0.50 x 0.55 x 18). This equates to 11,000 additional smears, 880 abnormal smears, and 187 colposcopies per case of cervical cancer avoided. The Committee feels that these ratios are disproportionate.

The drawbacks of reducing the entry age would be made even worse by a switch to hrHPV screening.[284] Young women are especially likely to have a positive hrHPV test (Table 1, page 26). They tend to have a high incidence of transient hrHPV infections.[178] Specificity (for CIN2+) is significantly lower in those below the age of 30 than in older women.[89,170,284] If any abnormalities do occur, these are very likely to undergo spontaneous regression. As a result, false positive screening results are particularly common, as are the overdiagnosis and overtreatment of regressive CIN2.[131] Treatment can have an adverse outcome in subsequent pregnancies, but is generally limited to cervical loop excision, which does not involve an increased risk of serious obstetric complications, such as perinatal mortality or extremely premature birth.[136]

The Committee sees no reason why the current age limit of thirty should be lowered.

Upper age limit

Is the current upper age limit of sixty still adequate? It has been repeatedly argued that screening could reasonably stop for 50-year-old women who have had a number of consecutive negative smears. The evidence put forward to support this is that these individuals have a significantly smaller risk of CIN2+ than younger women (below the age of 50) with the same smear-test history.[289-292] While this is indeed the case,[293] it is also true that high-grade CIN in older women more often leads to cervical cancer than it does in younger women.[39,294] If cervical cancer is used as a measure of outcome, it appears that – after a number of consecutive negative smears – there is no difference between older and younger women in terms of their cancer risk.[293] This is consistent with the finding that hrHPV infections are relatively common in women over the age of fifty (Table 1, page 26).[295,296] It has also been determined that hrHPV-positive women over the age of forty have a much greater risk of developing cervical cancer than those below the age of forty.[34] It therefore seems illogical for screening to be terminated before the age of sixty. This applies both to cytological screening and hrHPV screening.

Are there any arguments to support an extension of the age limit beyond sixty? No studies have been carried out into the potential usefulness of such a measure. What is clear, however, is that the reduction in the risk of CIN2+ is

more pronounced and more protracted after a negative hrHPV test than it is following non-abnormal cytological findings. Sixty-year-old women who have only occasionally been screened, if at all, may well benefit from screening.[90] However, an economic analysis has shown that an additional round of screening for all women above the age of sixty, regardless of their smear-test history, would be very inefficient.[106] This is because, in the context of making the screening programme more intensive, it would be more cost effective to adopt less protracted screening intervals than to extend the existing age limits. This means that the issue of raising the age limit above sixty would only arise following two to three times as many screening tests as allowed for in the proposed programme design. This would involve many additional false-positive screening results and follow-up tests. As a result, the incremental net cost per QALY would rise to well above the threshold of € 20,000 used in the Netherlands.

The Committee concludes that there is no reason to amend the current age limit of sixty. In the recommended programme design, women of forty, fifty and sixty with a positive hrHPV test, and negative cytology at triage and after six months are given an additional screening after a period of five years.

7.2.6 *Cytology as the primary screening method for 30-year-old women?*

Model calculations show that the continued cytological testing of 30-year-old women offers no benefits in terms of QALYs, or of preventing cases of cancer or deaths from cervical cancer. The Committee has nevertheless considered the question of whether cytological testing should be continued for such women. This is because 10.7% of women of that age have a positive hrHPV test, more often than women later in life (Table 1, page 26).[22] Cytological testing has greater specificity than hrHPV tests, especially in younger women. Do the potential health benefits of hrHPV screening compensate for the encroachment on people's quality of life caused by hrHPV screening at this age? The Committee has used a sample calculation in an attempt to quantify the pros and cons of this issue, as far as possible.

The population of 30-year-old women in the Netherlands numbers more than 90,000. Based on a participation rate of 55% (in 2008), 50,000 of these individuals will participate in screening. Assuming a positive results percentage of 10.7%,[22] 3.2% (1,600 women) will get a management recommendation for immediate referral, while 7.5% (3,750 women) will receive a management recommendation for a follow-up smear test (cytology after six months).[22] Partly

due to the large numbers of women involved, the Committee has attached considerable weight to the loss of quality of life.

Are there any compensatory health gains? In the 30-34 age group, an average of seven women die each year in the Netherlands, while seventy others are diagnosed with the disease. Take a situation in which hrHPV screening can prevent half of all cases of cervical cancer, or at least detect them at a very early stage, such that the five-year survival rate is virtually 100%. This would cause disquiet to a total of 153 women (5350:35) per prevented case of cervical cancer (46 immediate referrals and 107 women with a follow-up smear after six months). The Amsterdam model is slightly more favourable than this estimate (which is based on national figures), involving 26 referrals (rather than 46) per prevented case of cervical cancer. Seven to eight of these referred women would be treated for CIN2/3. The Committee considers these figures to be acceptable. In this connection, they took the following into consideration.

The additional yield produced by hrHPV screening is not a result of overdiagnosis. POBASCAM demonstrates that, in the first round, the extra yield produced by hrHPV screening is of clinical relevance.[25] If the trial's intervention arm (hrHPV and cytology) is compared to the control group (cytology alone) across two screening rounds (hrHPV and cytology in both trial arms in the second round), the total number of women with CIN3+ is found to be the same, however those in the intervention arm are detected earlier. This means that these abnormalities are not regressive, and therefore clinically relevant. This also applies to the subgroup of women aged 30-34.[185]

The continued cytological screening of 30-year-old women involves retaining a relatively insensitive screening test just as cervical cancer is starting to reach its peak incidence. This is also precisely the age at which the sensitivity and the protective effect of cytological screening are lowest.[88-90] Allowance must also be made for the possibility of an absolute increase in the incidence of adenocarcinoma in young women.[11,89,95] This type of cervical cancer, which has a poorer prognosis, is difficult to detect using cytological screening. However, it can be more readily detected using the hrHPV test.

Continued cytological testing would cause more disquiet among 30-year-old women than hrHPV screening. Cytological screening at this age results in abnormal results for 8% of subjects. Of these, 1.7% involve direct referrals, 4.4% are given a management recommendation for repeat smear tests at 6 and 18 months, while 1.9% are advised to return for a repeat smear after six weeks.[61] If the latter 1.9% (disquiet caused by a follow-up smear after six weeks) is disregarded, this involves about 3050 women (6.1% of 50,000). Assuming a sensitivity of 35% and a participation rate of 55%, the range of screening options

can detect 19% of the 70 (=13) women with cervical cancer at an early stage. This amounts to disquiet among a total of 235 women per case of cancer (3050:13).

The Committee recommends that hrHPV screening be introduced from the age of 30, rather than 35 (following cytology at 30). While it is fully aware that the disquiet resulting from hrHPV screening will affect even more women in this age group, the Committee takes the view that this is amply compensated for by the extra yield from hrHPV screening.

7.2.7 Anticipated screening results

In VUSA screen, 3.9% of the participants had a positive hrHPV test and normal cytology.[26] Accordingly, the proposed hrHPV screening with cytological triage is expected to result in 3.9% of the participants in the first round being advised to return for a follo-up smear after six months. In the current screening programme, this figure is 2.5%, however the follow-up period is eighteen months rather than six.

After a period of six months, one third of the hrHPV positive participants with normal cytology were found to have abnormal cytology,[125] and were therefore eligible for referral to a gynaecologist. In addition, 1.7% were immediately given a management recommendation for referral.[26] This brings the total referral rate in the first round to about 3%. This referral rate is lower than it would be without triage (5.1%) but much higher than in the current screening programme (1.3%). HrHPV screening involves a longer screening interval, however, which means fewer screening rounds. In spite of this, the number of referrals is increasing. According to the Rotterdam group's calculations (using a cohort model) a woman's risk of ever being referred increases from 3.3% to 3.5%.

7.3 Treatment

For details of the treatment options available to women with CIN or cervical cancer, the Committee refers to the Dutch Association of Comprehensive Cancer Centres' (formerly VIKC, now IKN) guidelines (www.oncoline.nl).

7.4 Measures to boost participation

7.4.1 Invitation policy, follow-up

The Committee recommends that:

- more GPs be involved in issuing invitations to women to participate in the screening programme, or in issuing reminders to those women who failed to respond to the initial invitation
- where possible, a specific date and time for attendance should be included in the letter of invitation, the reminder, and follow-up
- those who do not respond to the initial invitation should be sent written reminders after about six weeks, rather than waiting for six months
- follow-up after an abnormal screening test result should be improved.

7.4.2 Self-sampling

The Committee recommends that the offer of self-sampling be provisionally reserved for non-attendees, to whom it should be offered three to six months after the usual repeat invitation. This safety net plan requires careful introduction and evaluation. The Committee is aware that self-sampling is the subject of ongoing scientific research.[70] Given the nature of the results obtained to date, however, it feels that non-attendees should not be denied access to self-sampling. The Committee emphasises that it does not want women who do intend to participate in the screening programme to ignore their invitation in order to get a self sampling device, as this could have an adverse effect on the programme's ultimate participation rate and yield.

The effect of active provision of self-sampling devices to non-attendees on regular screening has not yet been studied. For this reason, the Committee recommends that careful consideration be given to the way in which information about self-sampling is phrased in the invitation letter for regular screening. A simple statement is sufficient, including a reference to the website of the National Institute for Public Health and the Environment (RIVM) for details of the pros and cons of self-sampling, and why further research is required.

The advantages of self-sampling are that women can sample vaginal material at a time of their own choosing, and that it spares them a visit their GP. However, any women who are found to be hrHPV positive (9%) will still have to visit their doctor for triage.

It is not clear whether there is any advantage in offering self-sampling to the entire target group (as opposed to non-attendees only), so that women may choose to test themselves at home, rather than go to their GP for an hrHPV test. The Committee advises conducting regional trials with a view to establishing whether this approach is preferable to its recommended screening programme design in terms of participation, yield, and cost-effectiveness.

7.5 Quality assurance

The Committee assumes that guidelines (issued by the various professional groups involved) for quality assurance in cervical cancer screening will be updated.[65,69] An updated edition of the European guidelines[58] is to be published in the near future.

Invitation system

Invitations issued by the GP have the advantages of a higher participation rate and improved selection of the target group. If screening organisations issue the invitations, there is a better chance that women will receive the right information. Also, policy changes are more easily implemented. The Committee therefore recommends that screening organisations and GPs should conclude contractual agreements on this matter. It recommends that the invitation process be reviewed, to do greater justice to the benefits for both parties.

Screening test

The sensitivity and specificity of the hrHPV test are determined by various steps in the sample processing procedure.[297] The first step involves the quality of the smear. The second step is that the sampled material is transported to the laboratory, where it is subjected to various treatments that may affect the test results.

HPV16 detection from one laboratory to another can vary by up to a factor of one thousand. The variation in HPV18 detection is even greater.[298] Measures must be taken to ensure the elimination (as far as possible) of any variation caused by laboratory-related factors or the way in which tests are performed. Commercial tests do not guarantee reliable results. In addition to the usual internal quality steps, such as the use of internationally recognised positive and

negative run controls, additional action is needed. Only a limited number of laboratories can guarantee reliable test results.

The Committee recommends that only reliable, clinically validated tests be used for screening and healthcare, and that the number of laboratories used be restricted to a maximum of one per screening region. First and foremost, a stringent quality policy will be needed. Anything that detracts from the quality of testing will render any additional health gains from the proposed screening programme null and void. Secondly, centralisation tends to limit laboratory costs (the economies of scale can run to several million euros).

7.6 Future-proof infrastructure for the screening programme

It has been shown that, in addition to detecting high-grade CIN at an earlier stage than cytology, hrHPV screening actually provides better protection against cervical cancer and the associated mortality. In the medium term, the Committee does not anticipate the arrival of any new testing methods that are scientifically sound enough to provide an alternative to hrHPV as a primary screening method.

7.7 Implementation study

On receiving any Health Council advisory report on screening programmes, it is customary for the Minister to commission a implementation study by the Centre for Population Screening (CvB) of the National Institute for Public Health and the Environment (RIVM), before making a final decision. In this connection, the Committee recommends that the following issues be addressed, in addition to its previous recommendations:

- the optimum invitation schedule for the transition to hrHPV screening (with different screening intervals)
- the advisability of using a reference laboratory, laboratory accreditation, and coded quality control samples
- the development of a chain guideline for the quality of the screening programme
- restructuring of the primary screening process and of follow-up
- including opportunistic screening in monitoring and evaluation, as this could increase if the screening interval is extended, thereby undermining the cost-effectiveness of the screening programme
- linking the registration of girls who have been vaccinated with the screening registries.

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A	Request for advice
B	The Committee

Annexes

Annex **A**

Request for advice

On 20 March 2007, the President of the Health Council received a request from the Minister of Health, Welfare and Sport for an advisory report on the prevention of cervical cancer. The Minister wrote (letter PG/ZP-2.746.254):

I hereby request that you advise me on the prevention of cervical cancer, in the light of new techniques and developments. This relates to new techniques in the screening programme, such as liquid based cytology and screening for human papillomavirus (HPV), as well as the availability of preventive vaccines against this virus. It was primarily the latter development that prompted this request for advice. HPV is a sexually transmittible virus whose presence goes unnoticed by carriers. Infections by certain types of this virus can lead to the development of cervical cancer.

Every year, about 600 women in the Netherlands are diagnosed with cervical cancer. In the 1990s, the Netherlands launched a nationwide screening programme for cervical cancer (the Pap smear test) for women aged 30 to 60. In this country, mortality from cervical cancer has declined by 33% since the start of this programme. Nevertheless, some 200-250 women a year die from the effects of this disease. Studies have shown that the effectiveness of a screening programme depends mainly on its ability to reach the target group. Overall, 77% of the target group are reached once every five years. Accordingly, the policy goal is to boost participation in the screening programme.

The screening programme's new techniques were broadly discussed in your 2006 Annual Population Screening Report. In a current screening trial, the effectiveness of conventional screening plus

screening for hrHPV is being compared to conventional screening alone. The results of this trial are expected in 2007.

In November 2006, an HPV vaccine was introduced to the market. The manufacturer claims that the vaccine protects against cervical cancer precursors and genital warts. The vaccine is registered on the Dutch market for use in girls/women and boys/men from the age of 9 upwards.

Given the results of HPV vaccination and the developments described above, I would ask you to advise me (on the basis of the current level of knowledge) on the possible inclusion of HPV vaccination in a national vaccination programme or in the National Immunisation Programme as part of an integrated approach to – and optimisation of – the prevention of cervical cancer in the Netherlands.

I would ask you to incorporate the following questions and points of special interest into your advisory report:

- the relationship between possible vaccination and the current screening programme for cervical cancer from the perspective of efficiency, effectiveness, and cost effectiveness in the short and long term
- the effectiveness and safety of HPV vaccines
- the target group for possible vaccination, distinguishing between the usefulness of vaccination for girls/women and boys/men in various age groups
- the need to make up ground in terms of vaccinating those who are not part of the target group at the time of introduction
- the cost effectiveness of HPV vaccination – incorporating the results of RIVM's cost-effectiveness study into vaccination against HPV
- draw a distinction between the cost effectiveness of preventing cervical cancer and that of preventing genital warts
- aspects of the provision of information, as this does involve vaccination against a sexually transmitted infectious disease.

I naturally expect you to include in your advisory process a consideration of any international developments in the field of cervical cancer prevention. I would ask you to deliver the advisory report at the end of 2007.
The Minister of Health, Welfare and Sport,
(signed)
Dr. A. Klink

Annex **B**

The Committee

- Prof. J. van der Noordaa, *chairman*
  Professor Emeritus of Virology, University of Amsterdam
- A. C. Ansink, MD, PhD
  Gynaecologist/Oncologist, Comprehensive Cancer Centre Netherlands
- M. van Ballegooijen, MD, PhD, *adviser*
  Epidemiologist, Erasmus University Medical Centre, Rotterdam
- Prof. I.D. de Beaufort, PhD
  Professor of Health Ethics, Erasmus University Medical Centre, Rotterdam
- Prof. P.J.E. Bindels, MD, PhD
  Professor of General Practice, Erasmus University Medical Centre, Rotterdam
- Prof. J.T. van Dissel, MD, PhD
  Professor of Internal Medicine/Infectious Disease, Leiden University Medical Centre
- P.G.H. Janssen, MD, PhD, *adviser*
  GP, Netherlands College of General Practitioners, Utrecht
- Prof. G.G. Kenter, MD, PhD
  Professor of Oncological Gynaecology, Centre for Gynaecological Oncology, Amsterdam
- Prof. M.E.E. Kretzschmar, PhD, *adviser*
  Theoretical Epidemiologist, Netherlands National Institute for Public Health and the Environment, Bilthoven, University Utrecht

- Prof. C.J.L.M. Meijer, MD, PhD, *adviser*
  Professor Emeritus of Pathology, VU University Medical Centre, Amsterdam
- H.E. de Melker, PhD
  Epidemiologist, Centre for Infectious Disease Control, Bilthoven
- W.G.V. Quint, PhD, *adviser*
  Molecular Biologist, DDL Diagnostic Laboratory, Voorburg
- A. Rendering, LL.M, *observer*
  Ministry of Health, Welfare and Sport, The Hague
- Prof. E.A.M. Sanders, MD, PhD
  Professor of Immunology and Infections, University of Utrecht
- W.A. van Veen, MD, *adviser*
  Physician, Delft
- N. van der Veen, PhD, *observer*
  Netherlands National Institute for Public Health and the Environment, Bilthoven
- Prof. H.J.C. de Vries, MD, PhD
  Dermatologist, Academic Medical Centre, University of Amsterdam
- Prof. A.L.M. Verbeek, MD, PhD
  Professor of Clinical Epidemiology, University Medical Centre St Radboud, Nijmegen
- K. Groeneveld, PhD, *scientific secretary*
  Health Council, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are

discussed, so that all members of the Committee are aware of each other's possible interests.