CervicalScreen Norway – A screening programme in transition

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ABSTRACT

An organised screening programme for cervical cancer (CervicalScreen Norway) was implemented in Norway in 1995. The overall aim of the programme is to reduce the incidence and mortality of cervical cancer, and the screening coverage should exceed 80%. Women in the target age group (25-69 years) are invited for screening every third or fifth year depending on whether the primary screening test is a cytology smear or an HPV (human papillomavirus) test.

Since the initiation, there have been major changes within the programme and HPV testing has become increasingly important. The primary screening test has changed from cytology for the whole target age group to primary HPV testing for women from the age of 34, HPV genotype information is directing the follow-up of women in the screening algorithm, and HPV self-sampling will be implemented to increase attendance in under-screened women.

CervicalScreen Norway has had a significant impact on reducing the incidence and mortality of the disease. Nevertheless, there has been an increase in incidence in Norway the last decade, in particular among young women. In 2018, the WHO Director-General announced an ambitious global call for action to eliminate cervical cancer through vaccination, screening and treatment. CervicalScreen Norway supports the ambition of the WHO and is working towards this goal.

INTRODUCTION

Cervical cancer is the fourth most common cancer among women worldwide and the fourth leading cause of cancer death, with around 604 000 estimated new cases and 342 000 deaths in 2020, and with wide geographic variation.[1] Almost all cervical cancers are caused by high-risk HPVs (human papillomaviruses),[2] and today cervical cancer is considered a preventable disease through highly effective HPV vaccination and screening programmes, preferably with HPV-based tests.[1]

The European guidelines for quality assurance in cervical cancer screening give recommendations for cervical cancer prevention and control, pinpointing the important role of HPV primary testing and HPV vaccination.[3] Well-organised screening programmes have since they were introduced produced profound decreases in incidence and mortality of cervical cancer in many countries in Europe, Northern America and Oceania.[1,4]

An organised screening programme for cervical cancer (CervicalScreen Norway) was implemented in Norway in 1995, and the proportion of cervical cancers prevented by screening was estimated at about 70% in 2015.[5] There have been major changes within the programme since the beginning, and HPV testing has become increasingly important. The primary screening test has changed from cytology for the whole target age group to primary HPV testing for women from the age of 34 years. HPV genotype information is directing the follow-up of women in the screening algorithm, and HPV self-sampling will be implemented to increase attendance in under-screened women.

A BRIEF HISTORICAL OVERVIEW

The cytology smear (Pap-smear) was introduced as a diagnostic screening tool in the 1950s (Figure 1). Although Norway was the last of the Nordic countries

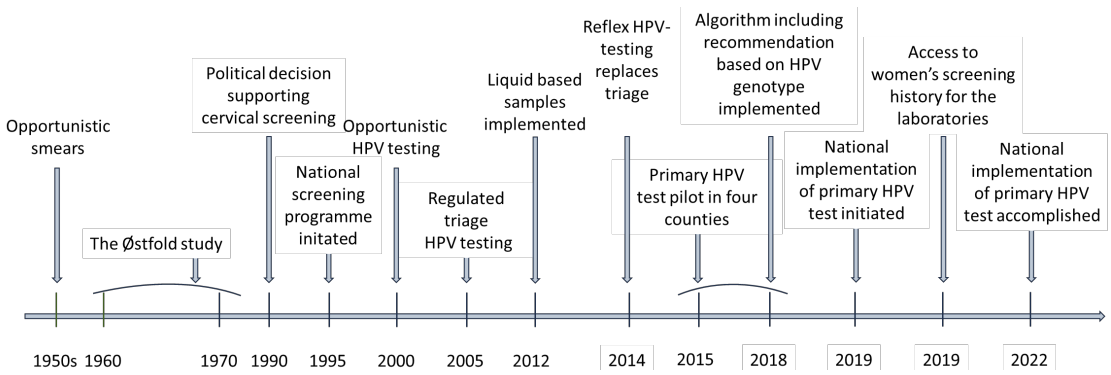

Figure 1. Important milestones in CervicalScreen Norway.

to introduce organised screening, a pilot project for evaluating the effect of mass screening was started already in 1959 in Østfold county. Five screening rounds were performed during 1959-77, and the cervical cancer incidence and mortality were reduced by 22% and 17%, respectively, in the target group.[6] However, this early initiative did not contribute substantially to establishing a national screening programme. In the 1970s and 1980s, the spontaneous screening increased steadily in Norway, but had limited effect on the incidence and mortality.[7,8] In 1990, the Norwegian Department of Health and Social Affairs decided to start a national screening programme for cervical cancer with triennial screening for all women aged 25 to 69 years. During the first three years of the programme, all spontaneous cervical cytology in Norway was recorded, and a pilot project was introduced in two counties (Sør-Trøndelag and Vestfold) to evaluate the organisational aspects of screening, providing useful guidelines for the national screening which began in 1995. Financial support from the Norwegian Cancer Society was crucial for the establishment of national cervical cancer screening in Norway.

IMPLEMENTATION OF SECONDARY AND PRIMARY HPV TESTING

In 2005, HPV testing was introduced in the programme in the follow up (delayed triage) of women with low-grade squamous cell cytological abnormalities (ASCUS and LSIL) (Figure 1). Reflex HPV testing was initiated in 2014, and the screening algorithm was updated accordingly.[9] Liquid-based sampling is the recommended procedure in the screening programme, and was implemented during 2012-14. Liquid-based sampling is also a prerequisite for HPV-based screening.

In several randomized studies, HPV primary screening has proved to be more effective in detecting precancerous cervical lesions and preventing cancer than cytology screening due to the higher sensitivity of the test for high-grade premalignant lesions.[10-12] The high negative predictive value of the test further allows for extension of the screening interval. Randomised implementation of HPV primary screening in women aged 34–69 started in four Norwegian counties (Hordaland, Rogaland and Sør- and Nord-Trøndelag) in 2015.[13] Based on the results from the pilot study, the Ministry of Health and Care Services in 2017 decided that 5-yearly primary HPV screening should replace cytology in the programme for women aged 34-69 years (with preceding 3-yearly cytology screening for women aged 25-33 years). Since 2019, HPV primary screening has gradually been implemented in the remaining Norwegian counties and is expected to be completed by 2022.

The results from the pilot were also used to optimise the algorithm, and in 2018, the algorithm was further adjusted, taking HPV genotype information into account.

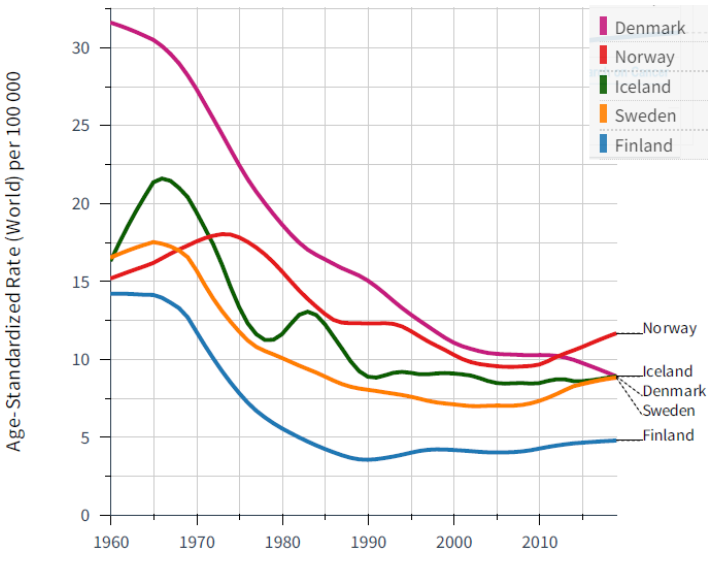

Figure 2. Age-standardised incidence rate of cervical cancer in the Nordic countries, 1960-2019 (NORDCAN database).

AIMS OF THE PROGRAMME

The overall aim of the programme is to reduce the incidence and mortality of cervical cancer within a systematic, quality assured population-based screening programme for women aged 25-69 years. The coverage should exceed 80% in the target age group. At the same time, over-use of services/excessive testing is discouraged.

In 2018, based on the availability of new preventive measures, the WHO Director-General announced an ambitious global call for action to eliminate cervical cancer. The aim is to reduce the incidence of cervical cancer to a rate below 4 per 100,000 women-years by vaccination (90% of all girls by the age of 15), screening (70% of women aged 35-45 years screened twice), and treatment (90% of women with precancerous lesions treated and 90% with cancer managed).[14] CervicalScreen Norway supports the ambition of the WHO and is working towards this goal.

TRENDS IN INCIDENCE

The development of the screening programme in Norway is partly reflected in the cervical cancer incidence. Figure 2 shows the incidence rate of cervical cancer from 1960 until 2019 in the Nordic countries. The decrease in incidence has been smaller in Norway than in the other countries.

Since the mid-1970 there has been a decline in incidence in Norway. During this period, opportunistic screening was widespread with frequent testing among selected groups, especially young healthy women, while older women were inadequately covered.[7,8] The sub-optimal distribution of testing led to an increase in incidence in the late 1980s, with a new drop from the beginning of the 1990s coinciding with the start of the national screening programme and a more evenly distributed testing of the female population at screening age. The curve flattened in the 2000s, and since 2013

Table 1. Number of cytology smears, HPV tests, histological samples, conisations and reminders during 2017-21.

Year	Cytology	HPV tests	Histology	Conisations	First reminder	Second reminder
2017	478 588	100 430	41 671	7 491	317 947	131 936
2018	422 275	117 519	42 858	7 512	336 346	146 175
2019	379 738	164 107	41 636	7 608	275 478	172 217
2020	356 978	193 275	42 864	7 515	317 516	140 678
2021	340 369	271 350	44 341	7231	320 341	151 556

there has been an increase in incidence, most pronounced in women below 35 years of age. This trend is of concern, and can be related to a sharp increase in cervical precancerous lesions since the 1990s, especially in women below 50 years.[15] The increases may again be associated with the rising levels of HPV prevalence in Norway,[16,17] which might reflect changing sexual habits.[18]

The most essential tool to reverse this trend is HPV vaccination. In 2009, HPV vaccination was introduced in the Childhood Immunisation Programme for girls in primary school (7th grade/12-year-old girls), and for boys at the same age in 2018. Consequently, the first female HPV vaccinated cohort will become eligible for screening in 2022.[16] In Norway, a bivalent vaccine (Cervarix) is presently used in the Immunisation Programme, and the vaccine coverage is very high (above 90%). The implementation of HPV primary screening and high HPV vaccination coverage are important initiatives to meet the global call for action towards elimination of cervical cancer as announced by the WHO in 2018.[14] A recent model-based analysis projected that Norway will achieve cervical cancer elimination by 2039 under the current HPV vaccination and screening policies.[19]

AGE OF THE TARGET GROUP

European guidelines recommend that cervical cancer screening should start from 25-30 years using cytology as primary screening test.[20] HPV primary screening should not begin under age 30 years due to detection of HPV infection of no clinical significance and overdiagnosis of CIN (cervical intraepithelial neoplasia) 2 that would have regressed spontaneously. HPV primary screening is, however, recommended at age 30-34 years or above.[3] The upper age limit recommended for screening is 60/65 years irrespective of primary screening test. In CervicalScreen Norway, women are invited to cytology screening from the age of 25, and thereafter to HPV primary screening from the age of 34. The upper age limit of the programme is 69 years.

Based on a request from the Norwegian Directorate of Health, CervicalScreen Norway in 2008 investigated if the upper age limit should be changed from 69 years to 65 or 60 years, and if the screening interval should be extended from 3 to 5 years for women older than 50 years.[21] The estimated increase in the number of cervical cancers and the risk of CIN 2/3 following these changes were considered not to be in proportion to the marginal savings. Thus, the suggested changes were not recommended in the programme.

ORGANISATION OF THE PROGRAMME

CervicalScreen Norway is an integrated part of the national health care system and is run by a central unit (the Secretariat) at the Cancer Registry of Norway. The programme receives mandatory reports from private as well as public pathology and microbiology laboratories, and it keeps complete records of the results from all cytology smears, histology specimens as well as HPV tests. Individual screening data are recorded and organised into four sub-registries; the Cytology Register, the Histology Register, the HPV Register and the CIN Register, the last holding follow-up and treatment data. Mainly general practitioners and gynaecologists take the cervical samples, while pathology departments and microbiology laboratories around the country are involved in screening the smears and analysing the HPV tests.

The Advisory Board of CervicalScreen Norway, established in 2001, gives advice to the programme and is authoring the Quality Assurance Manual. The Steering Committee, established by the Norwegian Directorate of Health in 2009, is supervising the programme.[9]

ACTIVITY

All women receive an introductory letter with information about the programme and an invitation to participate the year they turn 25. The screening programme is based on reminders, and personal letters (reminders) are sent to women aged 26-69 years who have no cervical sample recorded for the past three/five years. Reminders are also sent if cervical samples displaying dysplasia/abnormalities/HPV positivity and cervical samples with insufficient/unsatisfactory material are not followed up according to the guidelines (Table 1).

The women have the right to object to the storage of information related to normal test results in the screening programme. They also have the right to object to the sharing of test result history with healthcare professionals who request access to it when treating the women. By 2022, 25 255 reservations/refusals/opt outs (25-69 years) have been made.

COVERAGE

A high population coverage is crucial for an effective screening programme.[22] In 2021, the coverage level for screening was 71.3% within 3.5 years in the target age group (25-69 years) in CervicalScreen Norway (Figure 3), well below the desirable participation rate of at least 80%. From 2005, there was a decline in coverage. Since

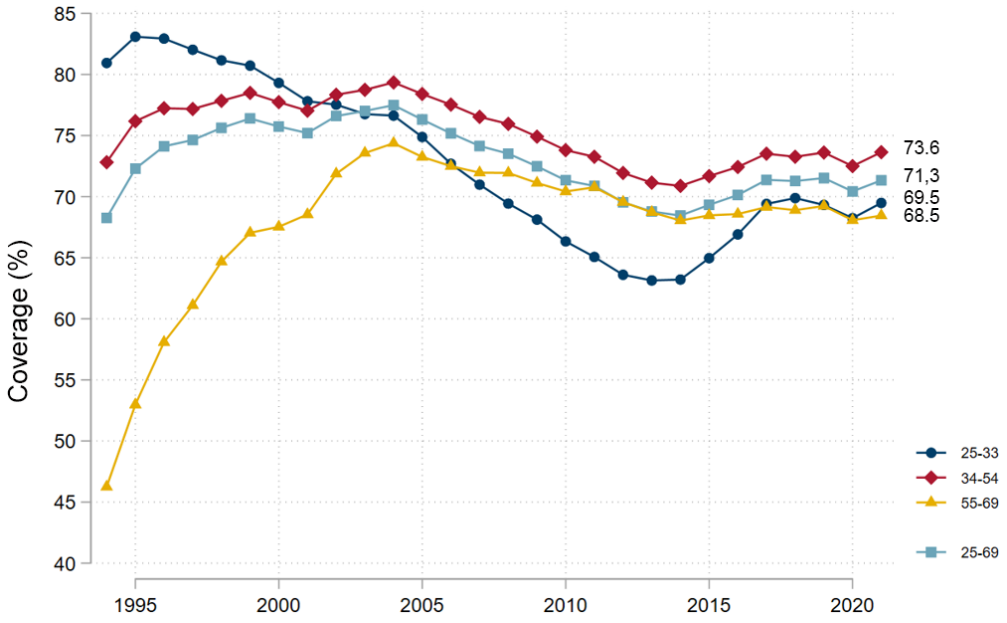

Figure 3. Screening coverage (%) within 3.5 years in CervicalScreen Norway by age, 1994-2021.

about 2015, however, the trend has been reversed, in particular among the youngest women (25-33 years). The coverage is highest in women aged 34-54 years and lowest in women aged 55-69 years. In 2020, about 13% fewer women than anticipated underwent cervical cancer screening due to the COVID-19 pandemic and the strict regulations that were imposed.[23]

Since 2015, a yearly campaign ("#sjekkdeg" [#CheckYourself]) has been carried out mainly targeting young women to increase attendance in the programme, and is run by the Norwegian Cancer Society. Also, information letters, videos and reminders have been translated into different immigrant languages such as Polish, Urdu and Somali, to increase screening participation in various minority groups.

Several studies indicate that HPV self-sampling may improve screening participation in under-screened women.[24-26] In 2022, a project aimed at implementing HPV self-sampling was funded by the state budget. Women with no screening test registered during the last 10 years will be the first to be offered self-sampling.

COMPARISON AND COLLABORATION WITH OTHER NORDIC SCREENING PROGRAMMES

In the Nordic countries, organised screening programmes have successfully reduced the cervical cancer incidence.[27] However, the implementation of organised screening has varied considerably between the countries.[17] Nationwide screening was implemented in the 1970s in Sweden, but not until the 1990s in Norway. Although there are many similarities between the programmes there are also differences.[28] The target age group for screening as well as the screening interval differ by country. The primary screening test is either cytology or HPV test depending on the age of the women.

The Nordic cervical cancer screening network has gathered national experts for annual meetings. NordScreen, an internet application presenting cervical cancer screening indicators in the Nordic countries, is important for quality assurance and improvement of the screening programmes.[28]

FUTURE PROSPECTS

It has been estimated that WHO's ambition of eliminating cervical cancer might be reached within a few decades in high-income countries with national screening and HPV vaccination programmes.[29] CervicalScreen Norway as well as the other Nordic screening programmes have had a substantial impact on the incidence and mortality of the disease. Nevertheless, there has been an increase in incidence in Norway the last decade, in particular among young women. Consequently, we need new efforts to reach WHO's goal by 2030.

Most cervical cancers are caused by a persistent, transforming infection with HPV, but the majority of women who test positive for high-risk HPVs do not have precancerous lesions. For HPV-based screening to function optimally, it is necessary to improve the specificity for CIN2+. Currently, all women with an HPV-positive screening test are triaged with cytology to separate those with high and low risk for cervical cancer. However, cytology is introducing over-diagnosis and over-treatment.

The majority of CIN will not progress to cancer, but solid guidelines for refined follow-up and treatment do not exist at present. Biomarkers that could predict the outcome of low- and high-grade premalignant cervical lesions are under development for clinical use.[30,31] A better stratification can be beneficial both for women with high risk of cancer, offering adequate treatment

and follow-up, and for women with low risk of cancer, reducing the need for close follow-up of low-grade lesions and over-treatment. Furthermore, the gynaecologists could reduce the current frequent follow-up of many women with a harmless HPV infection, and the pathologist would experience a reduced volume of low-grade biopsies. Overall, this would reduce unnecessary health care costs.

The first female HPV vaccinated cohort in Norway will reach screening age in 2022. At present, there are no international recommendations for how vaccinated women should be screened. Screening recommendations must be adapted to each country according to its vaccine coverage, time of vaccination initiation, level of catch-up vaccination and type of vaccine. Australia and Sweden have chosen HPV testing as the primary screening test, while Denmark and Norway currently use cytology in the youngest age group. In practice, there is an "infinite" number of screening algorithms that can be considered, as the primary screening method, screening interval, start and stop age for screening and triage analyses provide many possible combinations. In a model-based study, the health benefits and resource use associated with 74 alternative screening algorithms for HPV-vaccinated women in Norway were quantified.[32] It was concluded that less intensive strategies were needed for cervical cancer screening to remain cost-effective in HPV-vaccinated women, if individual vaccination status was identified and screening guidelines stratified accordingly, facilitating a personally tailored screening programme.

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