Special issue
Cancer Screening in Norway

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Introduction

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Background

Screening programmes against cancer represent an important part of the government’s cancer control efforts in several countries. The purpose of screening is to reduce the burden of cancer in the population by detecting and treating lesions before they become symptomatic. Treatment of precursors of cancer may prevent development of invasive disease and treatment of cancer at an early stage may prevent or postpone a fatal outcome of the disease. Screening is an example of secondary prevention of disease. Implementation of a screening programme in a region or country will depend on the organization of health services, culture and economy. International organizations such as the World Health Organization (WHO) and European Union (EU) recommend countries to establish screening programmes against cancer (World Health Organization, 2011; Council of the European Union, 2003). These organizations also support the work on guidelines for cancer screening and diagnosis (Perry et al., 2008; Arbyn et al., 2010) as well as handbooks of screening for different types of cancer (IARC Handbooks of Cancer Prevention Volume 7., 2002; IARC Handbooks of Cancer Prevention Volume 10., 2005). Opportunistic, non-programmatic screening is encouraged in many countries without organised screening, especially in the USA. However, to secure evaluation and quality assurance, the WHO and the EU Commission recommend screening activity to be organized in a programme as part of the public health services.

Public screening programmes have been part of the Norwegian National Cancer Plan in recent years (Norges offentlige utredninger, 1997; Helse- og omsorgsdepartementet, 2006). Currently, there are national screening programmes for cervical cancer (NCCSP) (Johansen and Bjørge, 2011) and breast cancer (NBCSP) (Hofvind and Skaane, 2011), and a pilot study on screening for colorectal cancer is being planned (Hoff and Bretthauer, 2011). Prostate cancer is the most common cancer among Norwegian men, but a general screening programme for this type of cancer has not been found tenable (Kvåle et al., 2011). In this world of rapid developments in medical science, the conditions for a screening programme might change due to new methods (Iversen et al., 2011), or by emergence of new preventive measures (Nygård and Iversen, 2011).

Screening

In screening, asymptomatic people are examined and classified as likely, or unlikely, to have a certain disease (Morrison, 1992). Those who appear more likely to have the disease, are investigated further to determine if they do. A diagnosis is usually not made during the screening examination itself unless the screening modality chosen is targeting visualization of structural changes, such as flexible sigmoidoscopy or colonoscopy screening for colorectal cancer. The quality of the screening device (test) is measured by its ability to separate the population into those who have and those who do not have the disease. Two measures commonly used for characterizing the test are sensitivity and specificity. Sensitivity is the proportion of truly diseased persons who have a positive test and specificity is the proportion of truly...
nondiseased persons who have a negative test. Even if these measures are very high i.e. close to 1.0, there will be some diseased persons with a negative test (false negative test) and some nondiseased persons with a positive test (false positive test). Both groups experience unfortunate aspects of the screening and the magnitude of these must be compared to the benefits. In a general population most diseases screened for are rare, i.e. the prevalence of the disease is low. In that case, there will be a large number of false positive tests, even with a test with high specificity. Most individuals with a positive test will actually not have the disease. For characterizing the combined effect of the screening test and prevalence of disease, two measures are useful: Positive predictive value (PPV) which equals the proportion of persons with a positive test that actually have the disease and negative predictive value (NPV) which equals the proportion of persons with a negative test that do not have the disease.

The screening concepts above are adapted from situations in clinical trials and laboratory medicine. In practical screening situations there might exist several options for defining some of the concepts (Hakama et al., 2007).

A prerequisite for screening is that the disease in question has a preclinical phase before symptoms occur, where the disease or precursor of the disease is detectable. This period is called sojourn time. The length of sojourn time will depend on the individual, the tumour and the screening device. In the case of screening for cancer the growth rate of the tumour is an important determinant of the length of this period. When screening is applied in a population, fast growing tumours are less likely to be found than less aggressive tumours. For tumours diagnosed through screening, the time from diagnosis till they would have been diagnosed without screening is called lead time. A further discussion of screening can be found in the following texts in English and Norwegian (Morrison, 1992; Tretli and Weiderpass, 2007).

**Principles of screening**

Several issues should be clarified before starting screening in a population. The discussion of pros and cons might end either way as demonstrated by the articles in this Special issue. The major principles of screening as formulated in 1968 (Wilson and Jungner, 1968) were:

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a “once and for all” project.

A prerequisite for implementation of screening is that the screening test has documented properties and is effective in reducing morbidity and/or mortality of the disease. Given that any screening method has both beneficial and harmful effects, the former must outweigh the latter. There should be a plan for managing and monitoring the programme to secure that it is in accordance with accepted quality standards. Participation should be voluntary and
potential screening participants should be supplied with adequate information for making an informed decision.

Evidence for screening
The scientific evidence for starting screening could come from a variety of experimental and non-experimental studies, but it is strongly recommended that randomized controlled trials (RCT) have been made to investigate the main effects of the proposed screening. Mammographic screening for breast cancer has been organized in many countries. At least six RCTs have been made for estimating the beneficial effect on breast cancer mortality due to inviting women to mammographic screening. The results of these studies have been summarized to show a 25% reduction in breast cancer mortality (IARC Handbooks of Cancer Prevention Volume 7., 2002).

Even if RCTs have demonstrated favourable effects of screening, further studies could be necessary for securing a successful introduction of a screening programme. For some programmes there is a demanding infrastructure which should be tested before launching a full-scale programme. In other cases, there is a need for comparing alternative procedures. This can be done in implementation studies. Screening against cervical cancer has for many years utilized a Pap smear as a screening test. In later years there have been several trials with a HPV test as a primary screening test. A Norwegian expert group has considered the scientific evidence for superiority of the HPV test as convincing. Consequently, they have proposed an implementation study in four counties, preceding a national programme for all nineteen counties. (Iversen et al., 2011).

Results achieved in a pioneer medical trial, cannot always be reproduced in routine health care. When starting screening there should be plans for how to evaluate the effects of the fully implemented programme. In some instances this has been done by starting the programme at different points in time for subgroups of the population and using randomization for selection of groups (Hakama et al., 1999). Others have used statistical models for estimating the effects of the programme when there has been a stepwise introduction of the programme (Olsen et al., 2005; Kalager et al., 2010).

Organization of screening
Screening should only take place within an organized programme. The very nature of this health service with both beneficial and adverse effects for the population calls for close surveillance of the population before and during screening. A careful registration of all activities is necessary, and such data should be readily accessible for those responsible for the programme. This is necessary for performing optimal quality assurance. For both screening programmes against cancer currently operating in Norway the responsibility for central coordination has been given to the Cancer Registry of Norway. In a report from January 2001 it was recommended that the national centre for cancer screening should be situated at the Cancer Registry (Sosial- og helsedepartementet, 2001). It is internationally acknowledged that there should be guidelines for each type of screening programme. Both for cervical screening and screening for breast cancer there are international guidelines that are periodically revised by international experts (Perry et al., 2008; Arbyn et al., 2010) These guidelines have been the basis for Norwegian quality manuals in the screening programmes (Kreftregisteret, 2003; Kreftregisteret, 2005). These manuals are revised by experts in the advisory boards of the programmes and contain guidelines for all types of work within it. Important parts of these guidelines are definitions of limits of process indicators for each part of the programme. If process indicators have unusual values, it might be an early warning that the programme is not functioning and adjustments should be made. In screening programmes for cancer in which reduction of cancer mortality is the main aim, there will often be an extended time period before any effect could possibly
be observed. In the meantime the surveillance of the programme has to be based on the process indicators (Hofvind et al., 2004).

**Basic elements for evaluation of screening**

An indispensable tool in the evaluation of screening against cancer is cancer registration covering the target population of screening. This registration should have been operating for a long period before starting screening in order to provide useful reference values. Some programmes are aimed at reducing cancer mortality; in that case the estimation of effect is dependent on an appropriate registration of cause of death. Since 1964 all citizens of Norway have been given a unique identification number. This has been used for registration of vital events and for events in major parts of social life. A centralized person register which is continuously updated, is available for administration and evaluation of screening programmes in Norway. All incident cases of cancer and some types of precursors have been registered since 1953 in the Cancer Registry of Norway. Registration of cause of death has for a long time been based on international recommendations and data from 1951 onwards is easily accessible. The incidence register and the cause of death register provide opportunity to study national and regional trends in cancer epidemiology. These registers contain identifiable information and are available for linkage to individual data from screening activities. Thus, some of the cornerstones for evaluating the effect of screening programmes against cancer are present.

Regrettably, Norwegian legislation does not give satisfactory conditions for administration, quality control and evaluation of screening programmes. Both programmes, NCCSP and NBCSP, started as scientific projects and were accordingly legally founded. These provided the opportunities for administration of the programme and evaluation of the results. Later on when the programmes had achieved national status, the screening activity was covered by Statutory regulations for the Cancer Registry (Helsedepartementet, 2001). These regulations demand that personal information on negative findings should not be kept for more than six months without active informed consent from the woman. The authorities subsequently decided that such consent had not been properly acquired in the programmes. The Cancer Registry was then told that it either had to obtain adequate consents by a certain time limit or delete the individual data. Deletion of data could seriously affect quality control and proper evaluation of mammographic screening. Moreover, the cervical cancer screening programme cannot be continued without keeping data on the screen-negative women for more than 6 months. The Ministry of Health and Care Services is working on a slight change of the legislation for the Cancer Registry, to allow the screening programmes to be run according to international recommendations. This legislation will hopefully be implemented this year (2011).

**Aspects of evaluation**

The results from the screening programmes can be regarded from different angles. For society that has initiated the programmes and is paying most of the expenses, the decrease in mortality and incidence in the total population is important. These results will depend on participation rate and should ideally be separated from the effects of screening outside the programme. One of the reasons for governmental engagement in the organization of screening, is the opportunity to secure equity in health services for the population. Statistics on participation by social class and region will give information whether such an aim has been achieved. Among those participating in screening there will be some who will have benefits, others will experience adverse effects. Estimates of these effects in the actual screening programme are needed by the health authorities who have the responsibility for evaluating these effects and decide whether the screening is worthwhile. These estimates should also be included in the information which is given to those eligible for participation in screening. They need facts for making their individual decision regarding participation.
There are some inherent difficulties in the evaluation of a national screening programme; the lack of a comparison group calls for making assumptions in the analysis that might be questioned. A national programme might have side-effects that should be considered when evaluating a programme. Cervical cancer screening is more integrated in public health services in Norway than in most national screening programmes. The programme performs follow-up of single patients and participates in quality control of work at the participating national laboratories (Johansen and Bjørge, 2011). Mammographic screening (NBCSP) was introduced in a stepwise fashion in Norwegian counties. Before entering the national programme each county had to establish multidisciplinary breast cancer care units, which probably have increased survival for breast cancer patients in all ages (Kalager et al., 2009).

**Improvement and changes in screening programmes**

From time to time it may be necessary to redesign screening programmes. Rapid development in medical knowledge may open for improvement in existing programmes or completely alter the panorama of prevention strategies within which the screening programme is a part. The HPV vaccination of younger cohorts of women will certainly have an impact on future screening for cervical cancer (Franco et al., 2006; Nygård and Iversen, 2011). Even with an effective vaccine there will be need for a cervical cancer screening programme and the results from the programme may be utilized in surveillance of the vaccinated cohorts. Less fundamentally, HPV tests have been introduced into different parts of the screening algorithm (Cuzick et al., 2008). New screening modalities have also been discussed in screening for breast cancer (Hofvind and Skaane, 2011). The introduction of these is in part connected to a discussion of selective use of screening modalities. For breast cancer there is currently a discussion on which age groups should be offered screening. For prostate cancer it seems that the effect of screening may depend on comorbidity (Kvåle et al., 2011).

The existing cancer screening in Norway includes only to a limited extent selective strategies. The access to background variables and complete screening history may open for even more effective screening programmes. Changes in screening programmes should be based on scientific evidence. Demonstration of the effects of a new algorithm can be a demanding process. Large samples and long follow-up are needed for stand-alone evaluation of cancer screening programmes. A running programme could be an appropriate setting for testing new modalities (Hoff, 2010). With a proper design the results from such experiments may give efficiency estimates of new methods relative to the older ones. Often this will be an easier task than demonstrating the efficiency in absolute terms. In many respects the infrastructure in Norway is well suited for such experiments since there are common national health services, several health registers and opportunity to link information from different sources. Nevertheless, in the case of cancer screening the knowledge and experience from other countries is important. Experiences from the Norwegian setting must be combined with evidence from other countries and international recommendations to make an optimal offer of cancer screening programmes to the Norwegian population.
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Introduction
Breast cancer is the most frequent cancer among women with an estimated 1.4 million new cancer cases diagnosed worldwide in 2008 (Ferlay et al., 2010). In Norway, between 2,700 and 2,800 women were diagnosed with breast cancer every year in the period 2001-2008 (www.kreftregisteret.no/no/Registrene/Kreftstatistikk/). The last decade, an additional 300 women were diagnosed with Ductal Carcinoma In Situ (DCIS) every year (Sorum et al., 2010). The incidence rate has declined from 2002 onwards; age adjusted (world) incidence rate in 2004: 77/100,000 women years: 2008: 73/100,000 women years. Breast cancer survival is influenced by stage at diagnosis. Five year relative survival for those diagnosed with breast cancer in 2004-2008 was 95% for stage I and 18% for stage IV. The mortality from the disease in women aged 45-64 years has been relatively stable between 46 and 56/100,000 women-years in the period 1980-1995, but a declining trend has been observed since the mid 1990s. The rate was 33/100,000 women-years in 2009 (www.norgeshelsa.no/norgeshelsa/). The causes of breast cancer are not well understood, but several risk factors have been identified. Hormonally related factors such as age at menarche, age at first childbirth, number of births, age at menopause and use of hormonal therapy are all well known risk factors, in addition to age, heredity, previous breast biopsy, height, weight, and other lifestyle related factors (Key et al., 2001).

Aim of mammographic screening
As there are limited efforts to prevent breast cancer, mammographic screening was introduced in order to detect the cancer in an early stage and thus reduce mortality from the disease. Several trials and service screening programmes have demonstrated that mammographic screening reduces the mortality from the disease (IARC Handbooks of Cancer Prevention Volume 7., 2002; Olsen et al., 2005; Paap et al., 2010; Gotzsche and Nielsen, 2011) and in 2002 the World Health Organization stated that there was sufficient evidence from randomized trials to recommend mammographic screening for women aged 50-69 years (IARC Handbooks of Cancer Prevention Volume 7., 2002). Further studies supporting the evidence have been published since 2002 and mammographic screening is implemented in most European countries today (European Commision, 2006). The target group is mainly women aged 50-69 years, but some countries and regions include from 40 to 74 years of age.

Benefits and harms of mammographic screening
There are benefits and harms of mammographic screening. The reduced mortality from the disease and breast conserving treatment, instead of mastectomy, are considered the main benefits. However, the effect of screening versus treatment on mortality reduction is still somewhat debated (Kalager et al., 2010) and the effects of screening and treatment in an early stage of the disease versus...
the effects of general improvements in diagnostics and treatment is still a matter of some controversy. Treatment is closely related to stage at diagnosis, and it might thus be impossible to separate these effects. Evaluating mammographic screening is a complex task where individual data on the first invitation to screening and adequate follow-up time are but two of several prerequisites for estimating the mortality. However, the benefits of mammographic screening are difficult to measure because most of them are not measureable on an individual level. After the introduction of organized mammographic screening in Norway, breast surgery has been centralized to 17 instead of previously 50 hospitals. All women with breast problems will benefit from this improved and consolidated knowledge and competence. Continuous surveillance and quality assurance of the work performance related to the screening programme ensure high quality of the screening service.

False positive and false negative screening tests, in addition to overdiagnosis and ionizing radiation exposure are considered harms of mammographic screening. A false positive screening test, (i.e. a positive screening test and a subsequent workup that does not show any malignancy) is considered a harm of mammographic screening because it often leads to anxiety and concern (Brett et al., 2005). It is thus very important to keep the recall rate as low as possible. Studies have shown the psychological strain related to a recall to be transient and most women reattend two years later (Ekeberg et al., 2001). However, most probably a recall including a biopsy is more stressful than a recall including additional imaging only. False negative screening tests might lead to delayed diagnosis and less favourable prognosis. Continuous quality assurance is recommended to minimize the problem, which has to be considered a part of all screening programmes, and for breast cancer, mammography is the only test that has proven to reduce mortality. Overdiagnosis is defined as the detection of breast malignancy at screening that would have never clinically surfaced in the absence of screening. Overdiagnosis might be mirrored in the incidence of the disease and is related to the natural history and lead time of the disease and exists both for screening and diagnostic mammography.

Administration and logistics of the Norwegian Breast Cancer Screening Programme (NBCSP)
The NBCSP started as a four year pilot project in four counties (Akershus, Hordaland, Oslo, and Rogaland) in 1995/96. At that time, it was considered neither necessary nor ethically acceptable to do a randomized trial because several trials had shown convincing results in favour of screening. Dr. Steinar Thoresen, MD, was the head of the screening department at the Cancer Registry of Norway (CRN) at that time. After two years performance of the pilot project, the Government decided to introduce the programme nationwide as fast as feasible. In 2004, the last county was included in the programme. The NBCSP is run according to the European Guidelines and is targeting women aged 50-69 years (European Commision, 2006; Kreftregisteret, 2003). The women are invited by a personal letter to have a two view mammographic screening biennially. The invitation letter states time and place for the examination, in addition to serving as a source of information about benefits and harms of mammographic screening. The screening test takes place at 28 dedicated stationary and four mobile units. The mammograms are independently read by two radiologists. If one or both readers have interpreted the screening mammograms as positive and a subsequent consensus has stated the mammograms positive, the woman is recalled for further examination at one of 17 breast clinics established as a part of the NBCSP (Figure 1). At the breast clinics radiographers, nurses, radiologists, pathologists, surgeons, and oncologists are working together in multidisciplinary teams which are aimed at diagnosing and treating women with breast problems professionally.
The NBCSP is run in collaboration with the Government, the Cancer Registry, the National institute of Public Health, the Norwegian Radiation Protection Authority, and the five Health Regions. It is headed by the Ministry of Health and Care Services and administered by the Cancer Registry of Norway. The Registry is also responsible for quality assurance and control of performance measures and the data collected. Members of the staff are also represented in European and International networks and are taking part in several national and international research projects. A national advisory group has been included in different organization models since the pilot project started. Its aim is to support the administration and professions in the clinical aspects of the screening programme. Further, the National Institute of Public Health is responsible for the practical work of sending invitations, reminders and letters to all women with a negative screening test and the Health Regions are responsible for running the screening programme in each county, including screening interpretation, recall examinations, further diagnostics and eventual treatment and follow-up. The Norwegian Radiation Protection Authority is responsible for the quality control of technical equipments used in the screening and work up.
The present

Participation

As of January 2011, close to 2.5 million invitations had been sent to women in the target group of the NBCSP, and close to 1.9 (76%) million screening examinations had been performed (Figure 2). About 700,000 women have received an invitation once or more. A high uptake is needed to maximize the benefit of the NBCSP. The participation rate among those invited varies by county. Hedmark had the lowest rate in the prevalent screening round (first) in 2003-2004 (2003-04: 63%; 2003-2009: 67%), while Oslo had the lowest rate in the subsequent screening rounds (2006-2007: 62%; 1996-2009: 64%). Other counties with low participation rates are Østfold (2001-2009: 73%) and Møre og Romsdal (2002-2010: 72%). The different participation rates might be explained by use of private clinics for mammographic examinations (opportunistic screening and diagnostic mammography) (Hofvind and Sanderud, 2010). Hedmark was the second last county to be included in the NBCSP, and unpublished quality assurance measures have shown that 40% of the women in Rogaland (first county in the NBCSP) had had a previous mammography (at private clinics or at a hospital) before they entered the NBCSP, while it was 65% for Hedmark and 80% for Vestfold (the two last counties included). Rogaland, Troms and Finmark, Sogn og Fjordane and Hordaland all have participation rates close to 80%. The county specific variation is mirrored in the rate of women who have notified the Cancer Registry that they do not want to be invited to the NBCSP. That rate is highest in counties with a high volume of private clinics and lowest in counties with no or only a small volume of such an offer. Use of private clinics will bias future evaluation of the efficacy of the NBCSP since the women are invited, but do not attend and have their eventual breast cancer diagnosed outside the screening programme in a later stage compared to those diagnosed in the screening programme (Hofvind et al., 2008). Today there is no systematic registration or surveillance of mammographic service at private clinics.

![Figure 2](image-url)

**Figure 2**

Participation in the Norwegian Breast Cancer Screening Programme given in % of the invitations sent from start up and until April 2011 by county. Approximate number of invitations sent is given above the bars. Month and year of start up of the screening programme in each county/area is in parenthesis after the county/area name. Red line is indicating the average participation rate (76.4%).
Recalls
Using independent double reading with consensus is probably the reason for a recall rate below 3% in subsequently screened women in the NBCSP (Table 1). Subsequently screened women have been screened previously in the NBCSP, while prevalently screened have their first screening test in the programme. The recall rate is lower in subsequently screened as in prevalently screened women because previous mammograms are used for comparison in subsequent screening examination. Also the women are older and thus have less mammographic dense breast which makes the mammograms easier to interpret. Between 15 and 20% of the recall examinations due to mammographic findings conclude with a breast malignancy after which treatment is recommended (Positive Predictive Value, PPV). The recall rate, adherent procedures, including waiting time for the procedures and the statements are regularly measured as a part of the quality assurance in the programme, to ensure they are kept at acceptable levels.

Detection of cancers
Between five and six cancers are detected in every 1 000 women screened in the NBCSP. The interval cancer account for an additional one to two cases per 1 000 screened (Table 1). Due to lead time, the detection rate is assumed to be about three times the incidence before screening was introduced in prevalently screened women (European Commision, 2006). In subsequently screened women the rate is expected to decrease to about one and a half the background incidence. These rough estimates are related to invasive cancer. Introduction of organized screening has led to an increased detection of Ductal carcinoma in situ (DCIS), which account for about 20% of the screen-detected malignancies and less than 7% of the interval cancers. The rate was less than 5% before the programme started. DCIS is considered a premalignant breast disease and the increased detection of DCIS is considered to be due to lead time. Therefore a reduced rate of invasive cancers is expected after a while. This is often referred to as stage migration. The progression of DCIS is not known today, but it is assumed that

Table 1
Number of prevalent and subsequent screens performed in the Norwegian Breast Cancer Screening Program in the period 1996-2007 and respective rates of recalls, biopsies, screen-detected and interval cancer

<table>
<thead>
<tr>
<th></th>
<th>Prevalent screens</th>
<th>Subsequent screens</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=540 135</td>
<td>n=997 721</td>
<td>n=1 537 856</td>
</tr>
<tr>
<td>Recall rate</td>
<td>4.8%</td>
<td>2.6%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Biopsy rate</td>
<td>2.0%</td>
<td>1.1%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Screen-detected cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal Carcinoma In Situ</td>
<td>0.11%</td>
<td>0.09%</td>
<td>0.10%</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>0.50%</td>
<td>0.42%</td>
<td>0.44%</td>
</tr>
<tr>
<td>Total</td>
<td>0.61%</td>
<td>0.50%</td>
<td>0.54%</td>
</tr>
<tr>
<td>Interval cancer*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal Carcinoma In Situ</td>
<td>0.01%</td>
<td>0.01%</td>
<td>0.01%</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>0.16%</td>
<td>0.15%</td>
<td>0.15%</td>
</tr>
<tr>
<td>Total</td>
<td>0.17%</td>
<td>0.16%</td>
<td>0.16%</td>
</tr>
</tbody>
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*Two years follow-up after screening test; followed to 2010
the majority of the DCIS-lesions will progress into an invasive cancer if left untreated (Virnig et al., 2010). The increased incidence of DCIS is observed worldwide and the topic has drawn considerable attention.

Tumour characteristics
The prognostic tumour characteristics of screen-detected cancers are favourable compared with the interval cancers and cancers detected outside the screening programme (Hofvind et al., 2008). The screen-detected cancers have a smaller tumour size, are less frequently grade III and lymph node positive. Survival is closely related to these parameters. Due to the smaller tumour size, a higher percentage of the women diagnosed with breast cancer in the NBCSP have breast conservative treatment compared to those diagnosed outside the screening programme (Hofvind and Skaane, 2011). This is according to the goal of mammographic screening.

Quality assurance
Continuous quality assurance has been performed since the programme started, both at the Cancer Registry and at the local breast centres. The results have been communicated on site visits, meetings, reports and scientific publications. More than 70 scientific papers and 20 reports are based on data from the programme. Three PhDs are partly or fully based on the data (H Wang, 2002, S Hofvind 2005, H Wedon-Fekjaer, 2008), and four more (RS Falk, IHR Hauge, M Kalager, and SR Hoff), are in progress. Unfortunately, only limited quality assurance and control have been performed based on data from the NBCSP the last two years. This is due to lack of regulations that make the Cancer Registry able to store data collected in women with a negative screening test for more than six months after her screening examination. Until the Cancer Regulation was introduced in 2002, the NBCSP had its own license which allowed the Cancer Registry to collect, store and use the data without time restrictions. The content of the license was not transferred completely into the Cancer Regulation. Due to this all women participating in the NBCSP have to be asked to sign an informed consent to give the Cancer Registry permission to store their data created from the screening programme. The collection of informed consent started mid 2008, and about 96% of the women participating in the NBCSP agree. The events concerning these regulations have required substantial resources from the Cancer Registry, particularly the NBCSP staff. We are now looking forward to further improve the organization of the NBCSP in order to achieve its aims.

The future
Introduction of mammographic screening in general, including the NBCSP has led to new knowledge about risk, detection, and treatment of early stage breast cancer.

Screening tools
Mammography is considered the best tool for population based breast cancer screening today, but other methods might be available in the future. Magnetic Resonance Imaging (MRI) has a very high sensitivity for invasive breast cancer and is in some counties the recommended screening tool for women at high risk. Studies have reported a sensitivity for breast cancer of 33% for mammography, compared with 80-91% for MRI (Kriege et al., 2004; Kuhl et al., 2005). For many years, MRI was suggested to have a low sensitivity for DCIS, but a recent report concluded that MRI had a comparable or even superior detection of DCIS compared with mammography (Kuhl et al., 2007). “Post-MRI second look ultrasound” will often identify a small tumour detected at MRI. However, if a small mass is neither identified on mammography nor on ultrasound, a MRI-guided vacuum-assisted biopsy, which is an expensive and time-consuming procedure, may occasionally be necessary. Experience from the last few years indicate that the problem of false positive MRI-findings probably are less than earlier suggested. Another advantage of MRI is no use of ionizing radiation.
It is well known that ultrasound, as an adjunct to mammography, may reveal many cancers missed on mammography in women with dense breast parenchyma (Berg et al., 2008). Automated whole breast volume ultrasonographic scanning systems (ABVS), now commercially available, may offer important advances for screening as compared with hand-held equipment. The examination can be carried out by trained technicians. The images are standardized and reproducible, and follow-up is therefore easier. Images can be interpreted in batch readings, and the interpretation time seems to be shorter for radiologists than with hand-held devices. In a larger prospective study, the number of breast cancers detected was twice as high when ABVS plus mammography was used as compared with mammography alone in women with dense breast parenchyma (Kelly et al., 2010). Limited data on the impact of Computer Aided Detection (CAD) in double reading programmes suggests that CAD has the potential to increase the cancer detection rates. Prospective studies in a screening setting are needed to evaluate the role of CAD input on the recall, biopsy and cancer detection rates. However, in double reading programmes of screening mammography (Gromet, 2008).

Advances in digital mammography have led to the development of digital breast tomosynthesis (DBT or “3D mammography”). This technique provides thin tomographic images of the breast and may reduce the obscuring effect of overlying and underlying tissue. DBT may have a potential in mammographic screening, either in a combined mode (FFDM plus DBT) or by replacing the conventional 2D images. Some few clinical studies published on DBT so far have demonstrated that DBT has the potential to increase both sensitivity and specificity in mammographic screening (Andersson et al., 2008). This early experience indicates that DBT may be of especial importance for the detection of small spiculated masses and distortions.

Screening based on individual risk factors
Age, heredity, mammographic breast density, previous breast biopsies, and hormonal factors are known risk factors for breast cancer. Several computer programmes and models are available to estimate individual risk profiles for breast cancer (www.cancer.gov/bcrisktool/) after which individualized screening intervals- and tool(s) can be recommended (Gail et al., 2007; Barlow et al., 2006). Based on available knowledge, the cost effectiveness of introducing individualized screening intervals and possibilities for a multimodality approach in the NBCSP should be investigated. The ethical aspects should also be taken into consideration. Women with a BRCA1 or BRCA2 gene, have a 50% to 85% lifetime risk of developing breast cancer. Recommendations for screening high risk women are established in Norway www.nbcg.no, but there is not yet an established surveillance or quality assurance system. Establishing a programme for registering the screening testing and follow-up in high risk women, as a part of the NBCSP, thus appears appropriate.

Expansion of the target population
Results from recent studies show a substantial reduction in mortality from breast cancer in women aged 40-49 years invited to screening (Hellquist et al., 2011). These findings indicate a need to consider the age group targeted in the NBCSP to be lowered to 45 years. Benefits and harms of an expansion should be discussed. Analyses of costs have been performed (Aas et al., 2007), but further, updated analyses are probably needed. There is also a need to ensure women 70 years and older effective diagnostics and treatment of breast cancer, when they are no longer invited to the NBCSP. The ability to be screened in the NBCSP should be possible for otherwise healthy women who want to be screened.

Complete database
A prerequisite to study the challenges related to the NBCSP and the heterogeneity of breast cancer is complete and valid data. Information about use of mammography and diagnostic work up in all Norwegian women provides a unique opportunity to study the overall efficacy of the NBCSP, the county and age specific diversity, and the natural history of breast cancer. Collecting uniform data
from all mammographic examinations performance is therefore needed. The unique possibility of linking this information with data from different Norwegian registries creates exclusive possibilities for internationally high quality research.

**Conclusion**
The NBCSP has run for 15 years with an overall participation rate of 77%, suggesting that women in general accept the harms associated with screening, in order to benefit from the early diagnosis. The cancers detected are prognostically favourable compared to cancers diagnosed before the screening programme started, but also compared to those diagnosed among women in the same age group who do not attend the screening programme. The NBCSP is run according to the European Guidelines, and preliminary results of early outcome measures make us expect a mortality reduction as a result of the programme. The programme will be evaluated by external research groups nominated by the Research Council of Norway. The evaluation will take place as soon as data become available, which is expected to be at the end of 2011. A concerted effort among all the specialties involved in screening, diagnostics and treatment of breast cancer is desirable to better understand the continuum of breast cancer care. The Cancer Registry of Norway holds experience and qualifications to be the coordinating organ, responsible for proper collection of data covering all aspects of the disease, including screening, diagnostics, and treatment, in addition to epidemiology, and biostatistics.
References


Cervical Cancer Screening in Norway

Bente Kristin Johansen and Tone Bjørge

The main objective of most cancer screening programmes is to reduce disease specific mortality. Because cervical cancer has a defined precancerous stage, cervical cancer screening also aims at reducing the incidence of cancer by detecting and treating women with cervical precancerous lesions which, if left untreated, could lead to cancer.

This article includes epidemiologic data of cervical cancer in Norway as well as a brief historic overview and a description of the screening activities, some results and finally a discussion of the adverse effects of cervical cancer screening.

Epidemiology of cervical cancer in Norway

While the incidence burden from cancer in general has been increasing the last decades, there has been a decreasing trend in both incidence and mortality from cervical cancer in Norway.

Figure 1 and 2 illustrate time trends in age-adjusted incidence and mortality rates for cervical cancer in the Nordic countries. From 1960 to 1975, there was a steady increase in incidence of cervical cancer in Norway. However, from the mid 1970s, a decline was observed parallel to the introduction of opportunistic screening. Around 1990 it seemed as if organised screening had lost its power, and an increase in cancer incidence was observed followed by a decline attributed to the implementation of the organised screening programme in 1995.

Figure 1
Age-adjusted incidence rates (per 100 000) of cervical cancer in the Nordic countries 1960-2008, (Source: NORDCAN, Engholm et al. 2009)
The decreases in incidence and morality rates in Norway occurred considerably later than in the other Nordic countries. This is most probably due to the fact that Finland and Sweden had nation-wide, organised screening programmes from the late 1960s. Norway, in contrast, had organised screening in only one county at this time (Hakama, 1982).

In table 1, the actual numbers of cervical cancers and deaths as well as precancerous lesions (CIN2 and CIN3) in Norway are presented together with information on incidence and mortality rates for the period 2003-2008.

Table 1
Number of cervical cancers, incidence rate, number of deaths, mortality rate, and number of CIN2 and CIN3 in Norway 2003-2008 (Cancer Registry of Norway, 2003-2008)

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
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<th>2005</th>
<th>2006</th>
<th>2007</th>
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</thead>
<tbody>
<tr>
<td>Number of cancer cases</td>
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<td>269</td>
<td>305</td>
<td>309</td>
<td>264</td>
<td>270</td>
</tr>
<tr>
<td>Incidence rate</td>
<td>9,5</td>
<td>8,7</td>
<td>9,8</td>
<td>9,6</td>
<td>8,4</td>
<td>7,7</td>
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<tr>
<td>Number of deaths</td>
<td>109</td>
<td>81</td>
<td>72</td>
<td>79</td>
<td>84</td>
<td>93</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>2,6</td>
<td>2,0</td>
<td>1,8</td>
<td>1,8</td>
<td>2,1</td>
<td>2,5</td>
</tr>
<tr>
<td>Number of CIN 2/3</td>
<td>3354</td>
<td>3203</td>
<td>3101</td>
<td>3236</td>
<td>3546</td>
<td>3469</td>
</tr>
</tbody>
</table>
Cervical cancer screening in Norway

In the 1950s, the Pap-smear was introduced as a diagnostic and opportunistic screening tool. An organised cervical cancer screening programme was first introduced as a pilot project in Østfold County (Magnus et al., 1987). The first two screening rounds took place in 1959–1965, and the last in 1974–1977. A cohort was followed up until the end of 1982. The observed incidence and mortality of cervical cancer were compared with women in five neighboring counties who were not offered organised screening. Women not participating in the screening programme had a 61% higher incidence of cervical cancer and a more than two-fold excess in the mortality rate.

During the 1970s and 1980s, the number of Pap smears taken increased steadily all over the country. At the same time, it became obvious that frequent and unorganised screening had limited effect on the incidence and the mortality rates and also at a gradually higher expenditure. In 1990, the Norwegian Department of Health and Social Affairs decided to start a national screening programme for cervical cancer, based on recommendations specified in NOU 1987:8 (Norges offentlige utredninger, 1987). From 1990-1993, all spontaneous cervical screening activity in Norway was recorded in a central registry. In addition, a pilot project was implemented in the two counties of Vestfold and Sør-Trøndelag, to evaluate the organizational aspects of the programme. An evaluation of the project revealed that coverage in the two counties was approximately 71% compared to 65% in the rest of the country. The overall experience from three years of recording and piloting was convincing with respect to coverage, and useful guidelines for a national screening programme was provided (Bjørge et al., 1992).

Aims of the programme

From the start in 1995, the overall aims of the Norwegian cervical cancer screening programme were to reduce the incidence and mortality from cervical cancer by 50%, compared to the incidence and mortality for the period 1990–1994, and also to prevent an escalation of the number of screening tests taken in the period of 1992-1994, before organised screening started. Furthermore, the coverage, that is the proportion of eligible women being screened every tree years, should be kept at 80%. Internal and external quality management of the cervical cytology laboratories should be optimal and in accordance with the demands of the European guidelines for cervical cancer screening (European commision, 2008). Hence, each laboratory is supposed to analyse a minimum of 15 000 screening tests yearly. Moreover, the laboratories are responsible for keeping the cyto-histological, cyto-virological and cyto-clinical correlations high. Sample takers should be informed about test results as soon as possible or at least within three weeks.

Organisation

Today, the cervical cancer screening programme is organised as an integrated part of the national health care system. A cytological specimen (Pap smear) is taken by general practitioners or gynaecologists. Approximately 390 000 women have 430 000 Pap smears taken every year (Kreftregisteret, 2008). The Cancer Registry of Norway (CRN) receives mandatory reports from private as well as public pathology and microbiology laboratories. The CRN keeps complete record of the results from the recommended and opportunistic Pap smears, the histology specimens as well as the HPV tests. Individual screening data with a personal identifier are recorded and organised into four sub-registries: the Cytology Register, the Histology Register, the HPV Test Register and the CIN Register; the last holding follow-up and treatment data.

The CRN runs the Secretariat of the Norwegian Cervical Cancer Screening Programme (NCCSP). The Secretariat keeps an administrative database which is based on the four sub-registries mentioned above. By monthly linkages to the external National Population Register, reminders (personal letters) are sent to women aged 26–69 who are not registered in the database with a smear or a test for the last three years. A second reminder is sent after an additional year if a test still cannot be traced. In addition, all women aged 25 receive an introductory letter with
information about the screening programme and an invitation to participate.
The smear takers are supposed to inform the woman and record if she does not approve registration of a personal identifier in the CRN, if the tests are negative. Positive screening results can be registered without consent according to Norwegian regulations. Women also have the opportunity to make reservations from receiving reminders. The CRN keeps a register containing all reservations, including those women who have reported their hysterectomies.

Biological material originating from screening is to be stored in a biobank linked to the particular pathology unit engaged in the screening activities. There are 20 units diagnosing cytology and/or performing histology diagnostics and 11 laboratories analyzing HPV tests, and some of them incorporate HPV genotyping. Since 2005, the CRN and the laboratories have used the Bethesda System of Classification (Solomon et al., 2002). The FIGO system is used for staging of cervical carcinomas (Sobin and Wittenkind, 2002).

So far, only four laboratories have converted to liquid based cytology; the remaining still practice conventional cytology, or are about to convert.

The laboratories are obliged to inform the physicians about the results and give recommendations for follow-up, and to transfer relevant data to the CRN. Information on screening and the screening programme is provided orally within the doctor-patient context. Women are also informed by letters, i.e. introductory letters and reminders sent from the Secretariat in the CRN. Furthermore, the screening programme keeps a website with extended information. It’s important to notice that women who have their smears taken at regular intervals will not receive reminders, and will therefore not receive any information by mail.

The Secretariat is guided in medical and screening questions by an Advisory Board with members from all expert fields involved in the screening activities. The Board is supervised by a Steering Committee established by the Norwegian Directorate of Health. The Advisory Board is authoring a Quality Assurance Manual and provides recommendations for screening algorithm, screening tests, evaluation, etc. (Kreftregisteret, 2005).

A flow chart illustrating the organization of the Norwegian Cervical Cancer Screening Programme is presented in Figure 3. Key characteristics of the Norwegian as well as the other Nordic programmes are summarized in Table 2.

Figure 3
Flow chart of the Norwegian Cervical Cancer Screening Programme
Table 2
Key characteristics of the Nordic cervical cancer screening programmes. NORDCAN.

<table>
<thead>
<tr>
<th></th>
<th>Target group (y)</th>
<th>Screening interval</th>
<th>Smears per lifetime</th>
<th>Incidence rates 2008</th>
<th>Mortality rates 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norway</td>
<td>25-69</td>
<td>3</td>
<td>15</td>
<td>8,7</td>
<td>2,1</td>
</tr>
<tr>
<td>Sweden</td>
<td>23-60</td>
<td>3 *</td>
<td>14</td>
<td>7,2</td>
<td>1,5</td>
</tr>
<tr>
<td>Denmark</td>
<td>23-59</td>
<td>3</td>
<td>13</td>
<td>11,2</td>
<td>2,1</td>
</tr>
<tr>
<td>Finland</td>
<td>30-60</td>
<td>5</td>
<td>7</td>
<td>4,2</td>
<td>1,2</td>
</tr>
</tbody>
</table>

*5-yearly at ages 50-60 years

Management of screen positive women
The Norwegian health authorities recommend women between 25 and 69 years to have a Pap smear taken every third year. Women with high grade cytology are directly referred for colposcopy and biopsy. Equivocal (ASC-US) and low grade (LSIL) cytology is the cut-off level for referral to a repeat or secondary smear and HPV testing after 6-12 months. If the secondary Pap smear is high grade, direct referral to colposcopy and biopsy is recommended. In the cases of negative HPV test in conjunction with a normal, unsatisfactory or ASC-US/LSIL secondary smear, regular screening after three years is the suggested action. If the HPV test is positive in conjunction with a secondary Pap test being ASC-US or LSIL, this should lead to colposcopy with biopsies. In the cases of normal or unsatisfactory secondary cytology and a positive HPV test, the woman is recommended another Pap smear and a HPV test after a period of 12 months. The recommendations for triage and the different follow-up strategies will be revised within the next year. The current management of screen positive women and the triage algorithm is illustrated in Figure 4.

Figure 4
Management of screen positive women. Flow chart showing algorithm of triage with HPV testing.
If the woman is not followed up according to the recommended procedures, the Secretariat contacts, depending on the diagnosis, either the woman herself, the laboratory or the woman's doctor.

**Reporting, monitoring and evaluation**

The participating pathology laboratories and gynecology units receive individual feedback along with standards of comparisons through yearly reports from the Secretariat and the Advisory Board. These reports include data from cytology and histology diagnostics together with results from diagnostic and treatment procedures. Performance or process measures or indicators monitoring activity and intensity, effectiveness, diagnostic assessment and treatment and laboratory results are monitored annually for providing early feedback in order to identify problems and to make necessary changes (Kreftregisteret, 2008). This is accomplished by linking the four cervical screening databases with the external Population and Cause of Death registries and with the internal cancer tumour registry of the CRN.

An audit by Bofin A et al (Bofin et al., 2007) of smear history in women with low-grade cytology before cervical cancer diagnosis was published in 2007. The authors showed that in a screening programme, a subgroup of smears may be diagnosed as unsatisfactory or low grade despite the presence of high grade findings that are detectable on reexamination. The following year, Haldorsen T et al (Haldorsen et al., 2008) published an evaluation of the programme which concluded that coordinated screening has contributed favourably in decreasing incidence and mortality rates as well as the number of tests taken. Furthermore, members of the Advisory Board evaluated in 2008 the preliminary experiences with HPV triaging and stated that there is a need for extended observation and further evaluation (Rådgivningsgruppen for Masseundersøkelsen mot livmørhalskreft, 2008). Hence, a second evaluation of HPV triaging is planned to be published in 2011.

However, it will be restricted by the current disability to use data from negative findings due to restrictions imposed by the Norwegian Data Inspectorate (see below).

Furthermore, the Secretariat completed an investigation of the possibility of lowering the upper age limit of screening and extending the screening intervals for women above 50 years. Based on data from the cervical screening registries, we concluded not to recommend any changes (Molden et al., 2008). A doctoral thesis by Nygård J in 2003, aimed at assessing the introduction of the coordinated cervical cancer screening programme and revealing possibilities to improve the guidelines, found that mailing recommendation letters only to women who did not take smears as recommended, provided a cost-effective solution (Nygard, 2005).

**Results**

The incidence and mortality rates of cervical cancer are presented above.

**Coverage**

A fundamental prerequisite for a successful screening programme is that women in the target population are actually screened. A population-based screening policy and organisation conforming to standards has to some extent had a positive effect on the coverage (Figure 5). Participation is highest in the age group 30 to 49 years and lowest in the oldest group (65-69 years). The positive effect which may be attributed to the organised and coordinated screening activities is a decrease (around 20 %) in the number of women under 25 years having had a Pap smear. Another possible explanation for this drop is that the Advisory Board actively has advised against regular screening for age-groups below 25 years. An additional positive effect is that after organising screening, participation by the oldest age group has increased by more than 20 % from the period of 1992-1995 to 2003-2006.
Incidence, coverage and number of smears before and after the introduction of organised screening

The positive effect of organised screening on incidence and mortality of cervical cancer has been pointed out in several publications. Early follow up studies among those invited to screening have indicated that the decrease in cervical cancer incidence was particularly pronounced among women participating in organised screening programmes (Magnus et al., 1987; Johannesson et al., 1982; Hakama and Rasanen-Virtanen, 1976). Peto et al (Peto et al., 2004) concluded that after 1988 and the introduction of a national screening programme in the UK, the rising trends of cervical cancer incidence and mortality were reversed. Figure 6 demonstrates the effect on incidence rate as well as coverage before and after the implementation of a nation-wide, population based screening programme in Norway in 1995.

The effect of streamlining cervical screening on the reduction of the total number of smears has also been demonstrated (Briet et al., 2010).

The same trend is observed in Norway after introduction of organised screening (Figure 7). The total number of Pap smears has been reduced by approximately 100 000 tests per year from around 542 000 tests in 1994 to 430 000 tests in 2008 (Kreftregisteret, 2008).

In 2007, we found that only 81 (31%) out of 258 women diagnosed with cervical cancer (all age groups) had had a previous test three years before the date of diagnosis, and 105 and 154 out of 258 had had a Pap smear four and ten years before, respectively (Kreftregisteret, 2008).

Adverse effects of cervical screening

Information on positive and negative effects of screening does not reach everyone, and the group that is supposed to benefit the most, i.e. the women not having Pap smears taken, is disturbingly hard to reach (European Commission, 2008).

In Norway, there is still a lot of opportunistic screening, especially among women under 25 years. On the other hand, we know that women above the age of 60 are tested too infrequently,
Figure 6
Cervical cancer incidence rates and coverage before and after organised screening (Cancer Registry of Norway, 2009).

Figure 7
Cervical cancer incidence rates and number of Pap smears before and after organised screening (Cancer Registry of Norway, 2009)
although improvements in both groups have been demonstrated (Kreftregisteret, 2008; Haldorsen et al., 2008).

Cervical screening tests can turn out to be false positive or false negative which might have unfavourable implications. False negative tests give rise to harmful personal consequences by implying false reassurance. False positive tests can lead to unnecessary follow-up tests, leading to both human and financial costs. In Norway, all women diagnosed with CIN2+ are recommended treatment. Annually, about 3,000 conisations are performed (Kreftregisteret, 2008). It seems obvious that some women are overtreated, as the likelihood of CIN3 progression into invasive cancer is estimated to be around 30% (McCredie et al. 2008). Excision of part of the cervix might have negative long-term effects. Sjøborg et al. found that odds ratio for giving birth before week 37, 32 and 28 after conisation compared to a control group were 3.4, 4.6 and 12.4 respectively (Sjoborg et al. 2007). In another study, Albrechtsen S et al. investigated cervical conisation and influences on outcome in subsequent pregnancies (Albrechtsen et al. 2008). Like Sjøborg et al., they observed an increased risk of preterm delivery, especially in the early gestational age-groups in which the clinical significance is highest. The relative risk of delivery was 4.4 at 24-27 gestational weeks, 3.4 at 28-32 weeks, and 2.5 at 33-36 weeks.

Cost-Effectiveness
A cost-effectiveness analysis was not carried out prior to the commencement of the organised screening programme in 1995, and none has been made since. Internationally, different models of cost-effectiveness support the message that organised screening is more cost-effective than opportunistic screening (Goldie et al., 2006; Chow et al., 2010). Obviously, there is a great need for evaluating the cost-effectiveness of the Norwegian Cervical Cancer Screening Programme.

Future prospects
The Norwegian cervical cancer screening programme will face fundamental changes in the future. Most importantly, new regulations for the collection and processing of personal health data in the CRN are announced, and will probably be introduced in 2011. Supposedly, this will alter the way the screening programme is organised and run. At present, there is no information available on the content of the announced new regulations, or how they will be operated.

In 2010, the Norwegian Data Inspectorate decided that the CRN is obliged to collect consent from all women screened in order to keep normal (negative) test results registered together with the personal identification data. If not, the CRN is forced to delete the personal identification attached to approximately 6 million negative tests from 1.5 million women. About 95% of the data recorded in the Cytology Register are from negative tests. The ultimate consequence of deleting 95% of these data is that the screening programme has to be terminated. This will also result in the loss of valuable data needed for research, quality assurance and evaluation. Triaging with HPV testing was established as a part of the official screening programme in 2005, and has led to a rather heated debate of whether it should have been implemented in the first place and secondly if it should be continued or not. The main issue of these discussions is which kind of HPV tests, DNA or mRNA, including the number of genotypes tested, is the most efficient and suitable for screening. Recently, the Norwegian Directorate of Health suggested restrictions for HPV tests to be used within the screening programme. It is expected that the Ministry of Health and Care Services in the near future will prepare a final conclusion on this long-lasting controversy.

In December 2010, the Norwegian Directorate of Health passed a proposal to the Ministry of Health recommending a pilot study evaluating the use of HPV tests instead of Pap test as the primary
screening tool. A prerequisite for converting to HPV based screening is that all laboratories involved have converted to liquid based cytology in due time. To augment transition, the health authorities introduced a reimbursement system for liquid based cytology in 2010.

From 2009, and subsequent to another long and heated debate, the Norwegian health authorities offered 12 year old girls free HPV vaccination. It’s expected that HPV mass vaccination will affect the prevalence of genital HPV infections, cervical precancers and cancers in the future. This will have a tremendous effect on how future screening should be organised. Nevertheless, screening of both vaccinated and non-vaccinated women will be needed for many years to come and it will be of great importance to integrate primary (vaccine) and secondary (screening) prophylaxis to form a comprehensive and effective programme for preventing cervical cancer in the future.

**Summary**

Implementation of a nationally coordinated cervical cancer screening programme in Norway has contributed to a lower incidence and mortality of the disease, to a more rational use of tests and a somewhat better attendance, especially among women older than 50 years. The effectiveness of organised versus opportunistic screening has also been demonstrated. The existing screening programme is facing challenges including the risk of being terminated. Continuation of a nationally coordinated cervical screening programme is strongly recommended also in the future.

**Acknowledgements**

Thanks to Gry B. Skare for providing tables and figures and to Rita Steen for guidance and contributions. Also thanks to Mari Nygård and Ole Erik Iversen for sharing their knowledge.
References


HPV primary screening in Norway: Recommendations for a controlled population based implementation study
Ole-Erik Iversen, Bjørn Hagmar, and Olav Karsten Vintermyr

Background
Cervical cancer is the second most frequent cancer globally. Even in European countries with well functioning screening programmes, the disease incidence ranks number two after breast cancer in young women (< 45 years). Today, it is well recognised that cervical cancer is caused by persistent infection with high risk HPV types, among which HPV type 16 and 18 accounts for 70% of all cases. At least 12-14 different HPV types have been shown to be oncogenic in humans.

Organized screening against cervical and breast cancer started in 1995. In contrast to the breast screening programme in which the major goal is to discover cancer at an early stage and to reduced mortality, cervical cancer screening also aims at reducing the incidence by detecting and treating severe precursor lesions (CIN 2 and CIN 3). There is solid scientific evidence that this strategy has been a success in many countries (McCredie et al., 2008). For equivocal smears (ASCUS, LSIL and inadequate smears) HPV testing in triage was recommended in 2005 and with a planned evaluation period for 3 years. A final evaluation of the benefits of HPV testing in triage for equivocal smears is still pending, however.

The scientific evidence for replacing cytology with HPV test
The primary strength of cytology is its specificity for detection of CIN 2+, whereas its main drawback is a relatively low sensitivity (of 50-60 %) for detection of CIN 2+ (Cuzick et al., 2006). The method may to some degree be subjective and reproducability has also bee shown to be suboptimal (Scott, 2002). HPV testing, on the other hand, as a more objective and reproducible method has a reported sensitivity for detection of CIN 2+ of 90-95%, based on various recent randomized clinical trials from several European countries (Leinonen et al., 2009; Bulkmans et al., 2007; Kitchener et al., 2009; Naucler et al., 2009; Ronco et al., 2010). Consequently, population based piloting HPV primary screening was recently recommended within organized programmes as a new screening option in the EU guidelines for screening against cervical cancer (Arbyn et al., 2010). Of particular importance, a negative HPV test result has a high negative predictive value for not having high grade cervical lesion so that the regular screening intervals may be increased without increasing the risk of CIN 2+ (Dillner et al., 2008). Of notice, these European trials show very consistently that more CIN 2+ cases are detected in the first screening round of the HPV arm (as compared to the conventional cytology screening arm), but a reduced detection of CIN 2+ in the following second screening round. The clinical significance of this observation is that women who will need treatment could be detected at an earlier stage without apparently more women being treated in total.

The high sensitivity of HPV testing for detection of CIN 2+ will be of particular significance in the near future when the HPV type 16/18 vaccinated cohorts of young women will enter ordinary screening age (25 year), because the prevalence of high grade cervical lesions will then presumably decrease drastically (Castle et al., 2010). A partial cross protection from vaccination against other hrHPV types may further add to a reduction in severe HPV induced cervical lesions.
The prevalence of HPV infection has risen sharply in many countries over the last 20-30 years and organised and opportunistic screening has prevented a high number of cervical cancers (Peto et al., 2004). In general, about 1 out of 3 premalignant cases (CIN 2+) will progress into invasive cancer if left untreated (McCredie et al., 2008). In Norway alone 3000 conizations for CIN 2+ take place yearly. Thus, an estimated number in the order of 600 - 1200 cervical cancers are prevented each year by organized screening.

The process so far
In the fall 2008, the Advisory Board of the National Screening Programme unanimously voted to perform an evaluation of a potential introduction of HPV testing to replace cytology as the primary test for screening in Norway. Prof. Hagmar chaired a committee (Group I) which already the next spring concluded that there was sufficient scientific evidence, based on clinical trials from several countries, to advice a population based implementation study to be conducted in Norway. The group furthermore gave a clear recommendation to the health authorities that a detailed plan for HPV test in primary cervical screenig, including a cost effective analysis, should be made. The recommendations were accepted by the Health Directorate, leading to a second group (Group II) to be established in the fall of 2009, initially chaired by Hagmar and later by Prof. Vintermyr. The group finalized a detailed project description, including a cost effective analysis, in November 2010. The proposed project was in December 2010 approved by the Health Directorate, which in turn made a recommendation to the Health Minister to have it considered for implementation in the trial population (Figure 1).

Details of the recommended population based implementation study
In accordance with the European Guidelines (Arbyn et al., 2010) demonstrations projects similar to postmarketing surveillance of new drugs (Phase IV studies), population based implementation studies are the logical next step for new diagnostic or therapeutic methods. The primary targets for such a proposed implementation study are:

1. To quantify potential health benefits with primary HPV based screening compared to the present cytology based screening.
2. Compare the participant attendance rate before and after introduction of HPV test
3. Evaluate logistics in clinical practice, laboratories and the Central Screening Unit in the Cancer Registry.
4. Evaluate benefits in use of other resources in the programme
5. Gain experience in the spread of relevant information to health personnel and the general public.

Details of the milestones for the proposed implementation study are presented in Figure 1.

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Figure 1
Milestones for the proposed implementation study
Based on favourable experiences from introductory pilot studies prior to nationwide implementation in both cervical and breast cancer screening programmes, the very same strategy was proposed for this implementation study. In the study, 4 out of 19 Norwegian counties have been selected (Rogaland, Hordaland, Sør-Trøndelag og Nord-Trøndelag), covering about 1 mill out of 4.9 millions totally in Norway. Close to 100% of all cervical smears are being examined in their local university pathology facilities in these counties, all of which have extensive experience in HPV testing (Vintermyr et al., 2008).

All specimens are planned to be liquid based, allowing for possible reflex testing, biobanking and additional scientific projects. Biobanking of aliquotes will facilitate posthoc analyses, and evaluation of the clinical potential for new biomarkers. A special discussion has taken place regarding whether to stratify the follow-up of HPV positive women based on HPV subtyping (HPV 16/18). Since results from randomised clinical trials on this issue is still insufficient and from the mere fact that HPV subtyping also adds further complexity into the screening algorithm, HPV subtyping has not yet been proposed as an integrated part of the screening programme.

The target population will be women aged 34-69 years. This means that they will in general have passed already three rounds of screening by cytology before entering the HPV based primary screening programme at 34 years of age. (Figure 2.). The total number of screening rounds after age 34 will thus be halved from 12 to 6. As can be seen from the milestones in the proposed project (Figure 2) a complete screening round of 6 years and 2 years for follow up is suggested before a final evaluation of the implementation study.

Figure 2
An overview of HPV versus cytology based primary cervical screening.
Follow up of HPV positive women

Based on whether the HPV tests are positive or negative a completely new follow up screening algorithm is proposed as shown in Figure 3. An average HPV positive rate of 8% was used for all age groups in the HPV screening programme for cost-effectiveness analysis. This should be a very robust basis for calculation of costs.

A HPV test applicable for the programme must meet some well defined and strict criteria as regards test performance and documented performance in clinical trials (Meijer et al., 2009). A minimum of the 12 most prevalent hrHPV types must be included in the test. A tender among providers of available HPV tests, meeting a set of strict performance criteria, will be recommended before a final decision on which specific HPV test to be selected for the implementation study. It is recommended that the same HPV test is used by all sites in the implementation study.

In countries having a well functioning cervical screening programme against cancer, a remaining main challenge for further improvements will be to increase the attendance rate, since the majority of cancers are seen in the minority (appr. 20%) who do not attend the screening programme. HPV test based screening does have an added possibility for home based self sampling. In this way unscreened women may be offered a simple self sampling kit suitable for mailing to the county laboratory for cervical screening (Gök et al., 2010). Results and experiences from the above mentioned implementation study will be presented in international scientific journals.

Cost-effectiveness analysis

HPV test in primary screening against cervical cancer will be cost effective when increasing the routine screening interval from 3 to 6 years as proposed in the presented implementation study. This has also been observed by others (Berkhof et al., 2010). Moreover, and not the least, primary cervical screening based on HPV testing will prevent more women from having cervical cancer than a screening system based on cytology as of today.

Process in 2011 and further

As mentioned above, the Health Directorate supported the plan in December 2010. As of February 2011 the proposed project is currently under consideration in both the Health and Finance Departments in the Government. Hopefully a decision can be made before the National Budget will be presented in the fall of 2011.
References


Cervical cancer: natural history and prevention

Cervical cancer is an infrequent end-stage of a series of changes that begin with infection with human papillomavirus (HPV) and range from minor cellular abnormalities to definitively pre-invasive lesions and invasive cancer. An HPV infection and its sequel in the population come in all sizes, from obvious cancers, down to symptomless but morphologically distinct intraepithelial lesions and infections that can be revealed only by a special microbiological test.

The natural history of cervical cancer is schematically depicted in Figure 1. Implicit is the notion that cervical cancer develops over a long period of time, starting with the infection with high risk (hr) types of HPV. HPV access the basal cells through micro-abrasions in the cervical epithelium (Woodman et al., 2007). After infection, HPV may be found in episomal forms, integrated forms, or both. Viral DNA replicates from episomal forms to produce new progeny virions, that are encapsidated and shed in the cervical lumen. The integration of HPV DNA into the host cell genome can lead to cellular transformation and development of cervical intraepithelial neoplasia (CIN). CIN is characterized by abnormal cellular proliferation, abnormal epithelial maturation and cytological atypia. To diagnose CIN histologically, nuclear abnormality is required to be present in full thickness of the epithelium and is graded as I, II and III, (CIN I, II, and III). These changes are most likely to regress, specifically in CIN I & II, (Castle et al., 2009; Nygard et al., 2006). While infection with hr HPV is necessary and indicates a biological onset of the disease, the HPV infection alone is insufficient for cancer development. Persistence of the infection over time increases the risk for further development of pre-invasive lesions (Kjaer et al., 2010). Clinically, this stage is asymptomatic and cannot be diagnosed without screening. Left untreated, almost one third of these lesions progress to invasive cancer during the next 20 years (McCredie et al., 2008). Along with cancer progression clinical symptoms appear, such as discharge, bleeding and pain. Appropriate treatment can cure the disease or postpone death, depending on the extent of the cancer stage at the time of diagnosis.

Obviously, cervical cancer is a disease which should be considered a continuum rather than dichotomous by its nature. Individual risk of being diagnosed with or dying from cervical cancer is dependent on where in the progress of natural history it has been diagnosed. If cancer is already present, the aim of the intervention is to postpone death; in the case of pre-invasive lesion, the intervention aims at stopping disease progression towards cancer. Intervention can also protect against the cause of the disease if given to the disease-free subjects. Measures for cervical cancer prevention have developed gradually, being closely linked to what is known about its natural history (Figure 1). Tertiary prevention refers to the treatment and rehabilitation of cancer patients in order to cure or improve quality of life. In cervical cancer the late-stage treatment is expensive and the outcome is poor. Since 1956 a five-year relative
survival rate of 10% has remained unchanged for patients with stage IV disease, while in 1997-2001 survival amongst patients with a stage I was >90% in Norway (Cancer Registry of Norway, 2007). In secondary prevention, through screening, individuals with asymptomatic pre-invasive lesions are identified (in pre-clinical phase of the disease) and treated to halt the process of cancer development. In organised programmes all women in defined age-groups are invited regularly to screening. Early diagnosis and treatment of cervical disease has proved to be a successful population strategy to combat morbidity and mortality associated with cervical cancer (IARC, 2005). However, as a secondary prevention, screening does not target the cause of cervical cancer, which is, as recently established, an infection with hr HPV. Prophylactic vaccines against hr HPV are now available. Immunization with highly efficacious HPV virus like particle vaccines protect against infection with HPV6/11/ and/or 16/18.

**Figure 1**
A hierarchical approach to cervical cancer prevention in Norway is presented in Figure 2. About 300 new invasive cancer patients are treated yearly in Norway. Approximately 60% of them are in an early stage with a good prognosis. As secondary prevention, yearly 3,000 women at high risk for cervical cancer are treated to prevent CIN II/III progression to cancer.

In order to determine this high-risk group about 450,000 screening smears are taken yearly from women aged 25-69 years. As a primary prevention of cervical cancer, mass-vaccination against HPV types 16/18/6/11 started in Norway in 2009, and girls at the age of 12 were offered free vaccine. About 70% of the 1984 birth-cohort has been vaccinated.

In order to prevent squamous cell cancers other than the cervix, HPV DNA is detected in different cancer types as summarised in Figure 3. About 40% and 80% of vulvar and vaginal cancers, respectively, are reported to be positive to hr HPV supporting the notion of mixed etiology of these cancers (De Vuyst et al., 2009b). The causal role of the HPV infection in oropharyngeal cancer is currently debated (Gillespie et al., 2009; Gillison et al., 2008). Increase of both HPV positive tonsil and base of tongue cancers, has
been reported in several recent studies (Attner et al., 2010; Mork et al., 2010; Nasman et al., 2009; Shiboski et al., 2005). The majority of the anal (over 70%) and penile cancers have been tested positive for HPV (Bleeker et al., 2009; Hoots et al., 2009).

HPV types detected in cervical cancers and pre-invasive lesions vary, being dependent on the geographical region and study sample type (general population versus high risk population). HPV16, the most common high risk type, has been reported to be present in 49-81% of pre-invasive lesions in cervix. HPV types 16 and 18 have been detected from 52-64% and 11-22% of cervical, 27-58% and 2-10% of vulvar and 46-77% and 3-27% of vaginal cancers, respectively (De Vuyst et al., 2009a; De Vuyst et al., 2009b; Garland et al., 2009; Insinga et al., 2008; Smith et al., 2009; Smith et al., 2007). HPV type 16 has been the most usual type detected from oro-pharyngeal, anal and penile cancers (Ang et al., 2010; Bleeker et al., 2009; Hoots et al., 2009).

Overview of the Prophylactic HPV vaccines
Since the publication of the highly effective HPV16 monovalent prototype vaccine in 2002, (Koutsky et al., 2002) two other prophylactic vaccines have been tested in Phase III trials and marketed. The bivalent vaccine protects against HPV16 and 18 (Paavonen et al., 2009) and the quadrivalent also includes HPV6 and 11, types that cause about 90% of genital warts (Munoz et al., 2010). Although they share the virus-like particle principle, differences in production and clinical trial details of the two vaccines do not allow direct comparisons between them, regarding many aspects of performance (Stanley, 2008). Broadly, both vaccines have been shown to be highly efficacious in preventing 90-100% of the HPV16/18 related CIN II and CIN III, and adenocarcinoma in situ. In addition to trials in adolescent girls and women, the quadrivalent vaccine programme also includes boys and men (Stanley, 2008). Second generation HPV vaccines against several other hr HPV types, have been in clinical trials since 2007, and are considered to be protective for about 90% of cervical cancer cases worldwide (Stanley, 2010). Duration of protection so far has been shown to be at least 9 years with the prototype HPV-16 vaccine, and immune memory has also been documented. Some cross-protection has been shown against closely related HPV types (eg HPV31 and 45) with both vaccines (Brown et al., 2009; Paavonen et al., 2009; Wheeler et al., 2009). Replacement with other genotypes, known to exist in bacterial infections, are under surveillance, but considered unlikely after HPV vaccination.

Epidemiology of the sexually transmitted HPV infection in Norway: timing of the prophylactic vaccination
No evidence of HPV infection among virgins, but a high prevalence of genital HPV DNA in young women shortly after sexual debut implies that genital HPV transmission probability is extremely high among HPV naive populations (Andersson-Ellstrom et al., 1996; Kim et al., 2011). However, the period of infectiousness cannot be very long, because of the rapid clearance of the infection. Hence, the proportion of persons to be immunised has to be high and the vaccination must focus on the whole population, not only on the sexually transmitted disease core group. In Norway, 4-years cumulative incidence of HPV infection among young females, 16-28 years of age was 25% for HPV16 and 14% for HPV18 in 1998-2005 (Kim et al., 2011). HPV16/18 prevalence among women less than 24 years of age was about 23% in 2007 (unpublished results) supporting the notion of the highly transmissible and rapidly clearable nature of HPV16/18 infection in young Norwegian females. Based on the literature, 52-67% of CIN II/III and 75-84% cervical cancer is attributable to infection with HPV16/18 (Insinga et al., 2008; Munoz et al., 2003; Smith et al., 2007). Given vaccines will eliminate all the HPV16/18 attributed CIN and cancer cases, assuming no cross-protection or replacement, the incidence rates would drop remarkably, as depicted in Figure 4.
Timing the prophylactic HPV immunisation shortly before sexual debut would be theoretically ideal for achieving best response and efficacy. However, it is difficult to define such an age precisely. Also, age at first intercourse has been subjected to change over time, well demonstrated by the questionnaire studies on sexual habits in Norway. The median age at first intercourse for males has been lowered from age of 19 for the birth cohorts 1927-1934 to age of 18 for the birth cohorts 1980-1984. This change was even larger for females, from 20 to 17 years of age, respectively (Stigum et al., 2010).

From the perspective of executing the mass-vaccination programme, the cost-effectiveness of the programme increases if the vaccine is given to age-groups before onset of sexual life, i.e before time of exposure to HPV. A very recent questionnaire study in 2004-2005 among females 18-45 years of age collected information about HPV infection and related risk factors. Less than 3% of women reported age of first sexual intercourse before the age of 13, 10% reported their first sexual intercourse at the age of 14, and 66% before 17 years of age (Jensen et al., 2011). Age 12, therefore seems to be justified, in the Norwegian context, to launch the mass-vaccination programme for optimal effect in terms of cost and public health benefit. However, it is unfair to assume that on an individual level, an onset of the sexual life itself is equal to contracting HPV infection. Many studies have showed positive correlation between hr HPV positivity and increasing number of sexual partners. Therefore, on an individual level, vaccination could be considered at ages older than that recommended in the childhood vaccination programme. In fact, many countries provide, so called catch-up vaccination in the enrollment phase of the mass-vaccination programmes, in order to provide protection to girls in older age cohorts, albeit with lower cost-effective gain. Alternatively, in some countries the vaccine is subsidized if given before a certain age to stimulate immunization outside the programme reducing therefore health inequalities between families who can and those who cannot afford this vaccine. Recently, immunization of women up to age 45 was reported to be highly effective (Munoz et al., 2009).

Generally, absolute numbers of patients with HPV related cancers is low, including anal, penile,
oropharyngeal and oral cavity cancers. Men who have sex with men and in particular HIV positive men are at high risk, even higher than the risk of cervical cancer in an unscreened population. Recently, an increase of HPV related oropharyngeal cancers have been documented in many countries, also in Norway (Blomberg et al., 2011; Braakhuis et al., 2009; Mork et al., 2010; Shiboski et al., 2005). Figure 5 depicts the temporal changes in crude incidence of cervical SCC in women and oropharyngeal SCC in men through a period of 1954-2008 in Norway. In boys, antibody titers are slightly higher after HPV vaccination than in girls of similar age. Clinical protective efficacy was recently reported also for men (Giuliano et al., 2011). So far, few countries have included boys in the vaccine recommendations. However, based on increasing disease burden, herd immunity aspects, better documentation of efficacy as well as reduced vaccine cost in the programmes; new cost effectiveness calculations should be made to update vaccination recommendations to eventually also include boys and men in the future.

Duration of vaccine effect
HPV vaccines became available in 2006, implying that documented duration of the vaccine efficacy is limited to the time of follow-up of the efficacy trial, i.e. about 4 years. The prototype HPV16 vaccine is the only one so far shown to be highly effective up to 9 years (Koutsky, 2009). Of particular importance was the finding that protection against HPV18 associated lesions was high even though only 60% of the women had measurable anti-HPV antibodies (Joura et al., 2008), indicating that presence of the vaccine induced immune memory cells. By vaccinating young girls at age 12, the effect is expected only about 10 years ahead. Whether there will be need for booster is a question yet to be answered.

Side effects of the vaccine
In clinical trials, the quadrivalent HPV vaccine was well tolerated in adolescent girls, young women and women 24-45 years of age. Fever, nausea and dizziness were the most common systemic adverse experiences, as measured in 1-14 days post-vaccination. Injection site adversities were measured in 1-5 days post-vaccination: pain and swelling occurred in 84% and 26%, respectively. These side-effects were mainly responsible for the slight increase
Serious adverse events were recorded in <1% of women 24-45 years of age (Munoz et al., 2009) and among 102 of 21 464 total subjects who received both quadrivalent vaccine and placebo (including 9-26-year-females and 9-15-year males). The most frequent serious adverse events were headache, gastroenteritis, appendicitis and pelvic inflammatory disease, rhinitis, vertigo, pulmonary tuberculosis, anemia, pyelonephritis, ectopic pregnancy and hepatitis, but none were vaccine-related. Slade et al. reported a study on vaccine safety on post-licensure period, following the distribution of more than 23 million quadrivalent HPV vaccine doses in the United States as of December 31, 2008. Data from the US Vaccine Adverse Event Reporting System for the 2.5 years following licensure were analyzed. The most frequent serious symptoms reported were headache followed by nausea, dizziness, vomiting, pyrexia, fatigue and syncope. Medically important serious events included 8 reports of anaphylactic reaction (1%), 9 deep vein thrombosis (1.2%), 31 Guillan Barré Syndrome (4%), 25 hypersensitivity (2.5%), 10 transverse myelitis (1.3%), 6 pancreatitis (0.8%), 14 pulmonary embolism (1.8%), 23 death (3%), 68 convulsion (8.8%), 30 urticaria (3.9%), and 9 autoimmune disorder (1.2%). The post-licensure safety profile was broadly consistent with safety data from pre-licensure trials, and most of the adverse event rates were not greater than the background rates and as compared with other vaccines (Slade et al., 2009). However, the continuous surveillance of adverse effects is of utmost importance to document the safety profile of any vaccine.

HPV type replacement and cross-protection
The impact of successful vaccination against HPV16/18 might introduce a so-called ecological niche for the non-targeted hrHPVs as shown in theoretical studies on bacterial vaccines (Lipsitch, 1997; McLean and Blower, 1993). According to considerations of evolutionary biologists, the equilibrium of different strains or sero-types of the same infectious agent in the population is a dynamic state and results from competition between the different types. Consequently, implementation of vaccination is expected to be followed by perturbation of the equilibrium between two or more types (Ewald, 1993; May and Nowak, 1995; McLean, 1995; Nowak and May, 1994). However, the presence of several HPV types in one person suggests little competition between HPV types, and therefore this scenario is likely not-applicable. In fact, several recent reports rather support evidence of cross-protection for non-vaccine included types (Ault, 2007; Paavonen et al., 2009).

Discussion
Cervical cancer is an infrequent long-term complication of otherwise transient and common HPV infection. To control cervical cancer, screening programmes are shown to be effective. However, there are several drawbacks of this strategy. Screening inevitably causes concerns about the health among women who perceive themselves as healthy. This concern is surely justified by the benefits, but is still a cost. Further, successful disease control can be achieved only by screening women regularly, in three year intervals, through a period of 45 years. This constitutes 15 screening visits per women, life-long, given that all visits are normal. Unfortunately, a screening test is, by nature imperfect, and cannot separate with 100% precision, those at risk. Consequently, several screening positives will be disease free; as well some who are ill will be screened as disease free. Another aspect is screening attendance and in Norway about 20% of women don’t follow the recommendations to take a screening test. The fact that 50% of cancers are rising from this population makes it extremely important to motivate women to regularly attend screening. In spite of all these obstacles, mass-screening for cervical cancer is one of the most cost-effective prevention measures available in fighting cancer. The biggest advantage of the screening strategy is that preventive action is not applied on women with low risk of cancer. A woman with CIN II/III only needs to be treated, presumably appealing decision both for the women and doctor. Those who are not at higher risk do not need to be
treated as they can be assured at being low risk until next recommended screening round. The fact that screening is organised within the existing medical organisation also helps to bridge the separation of clinical service and public health. As in classical medicine, the doctors concern is directed to help those with complains, and not those with increased risk for disease. The acceptance of preventive responsibility by clinicians is prerequisite to keep prevention within the mainstream of medicine.

However, cervical cancer screening contributes only little to overall control of all HPV related diseases. Availability of prophylactic vaccine, a primary prevention, therefore opens alternative possibilities to prevent both cervical and other HPV-related cancers by eliminating the widespread cause, an infection with HPV. While HPV is an immediate cause of cancers, sexual behaviour determines the exposure to HPV. It has been stated that changes in sexual behaviour represents the biggest shift in social norms in the 20th century. The epidemiologic pattern of HPV infection in the population is a reflection of the sexual behaviour in given socio-cultural circumstances, and is both socially conditioned as well as depending on personal choices. Furthermore, increase of HPV induced tonsillar and anal cancers in men are in line in what is known regarding changes in sexual behaviour. Therefore, to provide vaccination both for males and females is both morally and medically justified if the goal is to prevent HPV related cancers, including cervical cancer. Theoretically, vaccinating both girls and boys against HPV would be a radical and powerful approach, which would lead to rapid decrease in HPV infections. Obviously, this expected gain in health would be observable only in many years ahead, and justifying the cost of vaccination of both sexes has proved to be difficult.

Obtaining societal acceptance for a vaccine can be challenging. Population-wide preventive measures offer disappointingly little immediate benefit to the individual, which reduces the motivation to be vaccinated. Therefore, rarely occurring possible side effects of vaccination should be carefully considered. The safety profile of the vaccine is thoroughly reviewed and continues to be in focus in post-licensure studies. Reports from clinical and post-licensure studies, however, show only minor vaccine-related localised side-effects. It should be underlined, that lack of evidence is not evidence of its non-existence, and careful monitoring of long-term side-effects of vaccination is of major importance. Currently in Norway the childhood vaccination programme offers vaccine only for 12 year old girls. This strategy does not aim to eradicate relevant HPV types as only 50% of the population at risk are targeted, and about 65% are effectively vaccinated. Neither is this strategy aimed at protection from HPV related diseases occurring in males. In cervical cancer prevention, however, the expected gains can be observable already in 2015-2017 by documenting reduction of HPV-related cellular abnormalities in young women attending to screening. However, how to combine primary and secondary prevention of cervical cancer effectively remains to be determined.
References


Cancer in Norway 2009 - Special issue


Colorectal cancer screening in Norway

Geir Hoff and Michael Bretthauer

Colorectal cancer (CRC) is the second most incident cancer in Norway. Each year, more than 3500 individuals are diagnosed with the disease (Cancer in Norway 2008) (Figure 1). Although there have been improvements in therapy of CRC, the prognosis of patients with CRC is still poor, with 5-year relative survival around 60% (NORDCAN, Engholm et al. 2009). There are no early symptoms or specific clinical signs for CRC, and we know very little about lifestyle-related risk factors. However, we know that the majority of CRC cases arise from benign precursor lesions in the large bowel, the so-called adenomas. Therefore, CRC is considered an interesting cancer with regard to screening, both for prevention and early detection of the disease. For a long time, Norway has been in the forefront of colorectal cancer screening research. This review outlines colorectal cancer activities in Norway.

History of colorectal cancer screening studies in Norway

The first study on colorectal cancer screening in Norway was a feasibility trial using a guaiac-based faecal occult blood test (gFOBT) on a small population sample (n=754) performed by Jan Dybdahl in Bergen in 1982 (Dybdahl et al., 1984). The attendance rate was 55%, and one case of colorectal cancer (CRC) was diagnosed among 413 persons tested. In 1983 another small-scale screening study in Telemark county (n=400 invited) , using flexible sigmoidoscopy (FS) as screening modality, obtained 81% attendance and revealed one case of CRC and two cases of intramucosal carcinoma among 324 attendees (Hoff et al., 1985). This study, the Telemark Polyp Study no. I (TPS-I) showed a statistically significant 80% reduction in incidence of CRC at 13-year follow-up (Thiis-Evensen et al., 1999a). The TPS-I study was the first ever randomised controlled trial (RCT) on endoscopy screening for CRC worldwide (Figure 2).

Figure 2

Current endoscopy screening methods comprise colonoscopy (“gold standard” endoscopy screening as it may visualize the entire large bowel) and flexible sigmoidoscopy (“half-way colonoscopy” with a shorter reach endoscope and much simpler bowel cleansing procedure prior to examination). Colonoscopy reach: Combined drawn and interrupted lines. Flexible sigmoidoscopy reach: interrupted line.
Figure 1
Age-adjusted incidence rates for colorectal cancer in four Nordic countries 1965-2005. Denmark (DK), Finland (FI), Norway (NO), Sweden (SE). From (Larsen and Bray, 2010)
A colonoscopy screening trial initiative in the late 1980s in Norway and early 1990s in the US failed to materialise. Instead, a small-scale trial on colonoscopy screening was started in Telemark in 1996 as a continuation of the TPS-I study. A 62% attendance rate was achieved. Follow-up results regarding the effect of the screening intervention on incidence and mortality of CRC are expected in 2011. In 1999, the large-scale Norwegian Colorectal Cancer Prevention (NORCCAP) study was launched. During the period 1999-2001, more than 12 000 individuals were screened with FS in two areas in Norway, with an attendance rate of 67%. In 2009, preliminary results from the NORCCAP study showed a 27% non-significant CRC mortality reduction at 7-year follow-up (intention-to-screen analysis), and CRC mortality was significantly reduced by 59% for those attending (Hoff et al., 2009a). 10-year follow-up results are expected in 2012.

The first ever RCT on colonoscopy screening in the world was launched in 2009 (the Nordic-European Initiative on Colorectal Cancer, NordICC) with coordinating centre in Oslo and screening centres in Poland and the Netherlands. Norway joined with one centre in Kristiansand from January 2011. Thus, since the early 1980s, Norway has pioneered research on endoscopy screening for CRC.

<table>
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</table>

*flexible sigmoidoscopy
** approx. estimate from data given in the paper
*** CI not reported
Table 2
Characteristics of FOBT and flexible sigmoidoscopy screening

<table>
<thead>
<tr>
<th>FOBT</th>
<th>Flexible Sigmoidoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-70% compliance</td>
<td>30-70% compliance</td>
</tr>
<tr>
<td>80% false positive tests</td>
<td>No false positive tests</td>
</tr>
<tr>
<td>Annual or biennial screening</td>
<td>Screening every 5-10 years</td>
</tr>
<tr>
<td>*No cancer incidence reduction</td>
<td>23% colorectal cancer incidence reduction</td>
</tr>
<tr>
<td>15-20% colorectal cancer mortality reduction</td>
<td>30% colorectal cancer mortality reduction</td>
</tr>
<tr>
<td>5% screening positive require colonoscopy</td>
<td>5-20% screening positive require colonoscopy</td>
</tr>
<tr>
<td>Declining interest with time and screening rounds</td>
<td>Endoscopy screening gaining popularity</td>
</tr>
</tbody>
</table>

*Although FOBT is a screening method not designed for adenoma detection, a CRC incidence reduction was found in one RCT where the accumulated rate of colonoscopy with polypectomy on detection of adenomas approached 40% due to use of rehydrated FOBT tests and a very high rate of false positive tests (Mandel et al., 2000)

Evidence for CRC screening

The World Health Organisation recommends that screening programmes should be set up only when their efficacy has been proven in RCTs, and the EU Commission only recommends programmatic screening – not opportunistic screening which offers limited possibilities for quality assurance and evaluation (Advisory Committee on Cancer Prevention, 2000). For CRC screening, we now have follow-up results from randomised trials for FOBT screening (Hardcastle et al., 1996; Kronborg et al., 1996; Mandel et al., 2000) showing a 15-20% mortality reduction, and more recently, for FS screening showing a 30% reduction in mortality and 23% in incidence (Tables 1 and 2)(Atkin et al., 2010; Brethhauer, 2010; Hoff et al., 2009a).

Apart from FOBT and flexible sigmoidoscopy there are no RCT results on any other CRC screening modalities like colonoscopy, CT colonography and molecular markers in stool or blood. Although colonoscopy screening has been recommended for a number of years in the United States and many European countries, it is only recently that a randomised trial on colonoscopy screening was launched – the Nordic-European Initiative on Colorectal Cancer with its coordinating secretariat in Oslo (www.nordicc.com).

In Europe, opportunistic colonoscopy screening is now offered in Germany, Poland, Austria, Luxembourgh, the Czech Republic, Greece and Cyprus (Pox et al., 2007; Zavoral et al., 2009; Benson et al., 2008; Majek et al., 2010). Although the need for good quality randomised trials and evidence-based medicine is declared and taught, we do not always do as we preach (Table 3) (Hoff, 2010; Wilson and Jungner, 1968).

With screening, we are aiming to offer a health service, partly with highly invasive methods, to presumptively healthy people who may not even have asked for this service. No one would be allowed to market a new drug or treatment without extensive testing which includes randomised trials. Then it is hard to understand why standards for scientific proof should be set lower for screening services for a presumptively healthy population than for treatments for patients who do seek our advice “to the best of our ability and considering limited evidence”. It is understandable that patients are willing to accept limited evidence for the benefit of a health service when they are ill, but they should not accept a more extensive use of shortcuts on evidence for preventive and screening services.
Based on a simplified model regarding flexible sigmoidoscopy as a “half-way” colonoscopy, FS screening has been compared to performing mammography screening of one breast only – the preventive effect of endoscopy screening being considered to be merely a function of length of bowel examined – irrespective of left- or right-sided colonic segments. Baxter et al. challenged this by showing a CRC mortality reducing effect of colonoscopy for left-sided CRC only (Baxter et al., 2009). It has later been confirmed by Brenner et al. that prevalence of left-sided, but not right-sided advanced neoplasia,

<table>
<thead>
<tr>
<th>FOBT</th>
<th>Flexible sigmoidoscopy</th>
<th>Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>X (2009)</td>
<td></td>
</tr>
<tr>
<td>Bulgaria</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cyprus</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>X (2001)</td>
<td>X</td>
</tr>
<tr>
<td>Denmark</td>
<td>X (2005)</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>X (2003)</td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hungary</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Latvia</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Luxembourg</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Poland</td>
<td>X</td>
<td>X (2000)</td>
</tr>
<tr>
<td>Portugal</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Romania</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Slovak Republic</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Slovenia</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>X (2000)</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>X (2008)</td>
<td></td>
</tr>
</tbody>
</table>

*Recently decided after publication of UK randomized trial on flexible sigmoidoscopy screening (Atkin et al., 2010)
was strongly reduced within a 10-year period after colonoscopy (Brenner et al., 2010). If these findings can be confirmed, then colonoscopy screening may be of less benefit than expected in a public health perspective – maybe more comparable to flexible sigmoidoscopy requiring a less demanding bowel cleansing procedure. In that case, flexible sigmoidoscopy screening, with a higher attendance rate than for colonoscopy screening, may emerge more effective for CRC prevention than colonoscopy screening. However, this remains to be demonstrated. In 2010, shortly after publication of 11-year follow-up of a FS screening trial (Atkin et al., 2010), the British government raised funding to incorporate FS screening in their on-going national FOBT screening programme.

**Cost effectiveness**

As we only have limited knowledge of the size of an effect of CRC screening, cost-effectiveness estimates will carry a considerable degree of uncertainty. Treatment of advanced CRC has become extremely expensive as new cytotoxic therapies are emerging. The more costly such treatment is, the more attractive will screening and down-staging of CRC become. It has been estimated that an additional seven months survival achieved with the new drugs will be accompanied by a 340-fold increase in drug costs (Schrag, 2004). This has lead to estimates of colonoscopy screening being not only cost-effective and highly comparable to cervical and breast screening, but cost-saving compared to no screening (Sieg and Brenner, 2007).

**Organisation of a screening programme**

The EU Commission only recommends organised, programmatic screening (Advisory Committee on Cancer Prevention, 2000; Brenner et al., 2010) that can be evaluated aiming for continuous quality improvement. Improving CRC screening involves not only having tests with high sensitivity and specificity, but the screening modalities must be user-friendly and require few repetitive rounds (ideally once-only) to secure high uptake to make an impact in a public health perspective. The trade-off between these requirements was well demonstrated in a recently published Dutch study with a 1:1:1 randomisation between gFOBT, immunochemical FOBT (iFOBT) and flexible sigmoidoscopy (Table 4)(Hol et al., 2010).

Although the attendance rate was only 32% in the flexible sigmoidoscopy arm compared to 50% for gFOBT and 62% for iFOBT, the yield of advanced neoplasia per 100 invitees was significantly higher for a single round of flexible sigmoidoscopy screening than for either gFOBT or iFOBT. Considering current recommendations of less frequent rounds for flexible sigmoidoscopy (5-10-yearly) than for FOBT (annual or biennial), flexible sigmoidoscopy would clearly outperform gFOBT and iFOBT – at least in a Dutch public health perspective. This may turn out differently in other populations. National programmes should therefore have a responsibility to test screening modalities and attendance improvement strategies - continuously aiming to improve screening as a public health service.

**Table 4**

Randomised trial from the Netherlands showing compliance and “intention-to-screen” results of FOBT and flexible sigmoidoscopy screening (Hol et al., 2010)

<table>
<thead>
<tr>
<th></th>
<th>gFOBT</th>
<th>iFOBT</th>
<th>Flexible sigmoidoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. invited</strong></td>
<td>5004</td>
<td>5007</td>
<td>5000</td>
</tr>
<tr>
<td><strong>Attendance (%)</strong></td>
<td>50</td>
<td>62</td>
<td>32</td>
</tr>
<tr>
<td><strong>Advanced lesions per invitee (%)</strong></td>
<td>0.6</td>
<td>1.5</td>
<td>2.4</td>
</tr>
</tbody>
</table>
Combination strategies have been suggested. In the NORCCAP trial, the intervention arm was randomised 1:1 between flexible sigmoidoscopy only and flexible sigmoidoscopy combined with iFOBT (Gondal et al., 2003). The attendance rate was 4% lower in the FOBT arm, but iFOBT alone detected four of 20 screen-detected CRCs. Intention-to-screen analysis, however, showed no increased yield of 'high-risk adenoma' or 'any neoplasia' in the combined group. A Veterans Affairs Cooperative Study group reported that flexible sigmoidoscopy would detect 70.3% of all subjects with advanced neoplasia – increasing to 75.8% if adding a one-time screening with FOBT (Lieberman and Weiss, 2001). This 5% increase must be weighed against an expected drop in attendance rate. If attendance rate is not expected to be unduly compromised, then a combined flexible sigmoidoscopy and iFOBT strategy may be a good alternative to gold-standard colonoscopy or repetitive rounds of tests like FOBT depending on intermittent bleeding from ulcerated or eroded neoplastic surfaces. A US Preventive Services Task Force evaluation also concluded with a combined strategy being a good alternative to colonoscopy screening (Zauber et al., 2008).

Based on current knowledge, and acknowledging the Dutch attendance rates of 30-40% for FS with a potential to reach the Norwegian 60% level, the best CRC screening option at present seems to be FS after a single enema administered on site on attendance. The addition of FOBT would certainly have to be considered, but a 5% increase in detection rate of advanced adenomas must be weighed against a quantifiably expected or observed drop in attendance.

There is a multitude of screening modalities for CRC and more will come. This should be a blessing – forcing us to provide platforms for programme-based research to provide data and improvements on screening provisions much in demand from target populations and health care providers. According to an unpublished survey in 2007 by the International Digestive Cancer Alliance (IDCA) there were 6 out of 39 European states not having a national CRC screening programme or at least a pilot for such a programme. These were Russia, Ukraine, Moldova, Estonia, Malta and Norway. Norway is in the world “top-ten” league on CRC incidence and higher than any of these countries. The Norwegian national budget for 2011 now allows launching a pilot on CRC screening in two hospital areas. A choice of screening modalities may presently be of less importance than acceptance that national programmes must be given responsibility for continuously improving screening services including randomisation of screening modalities and strategies to improve population coverage.

Quality assurance

The EU Commission is concerned about poor quality screening and advice quality assurance at all levels – from invitation procedures down to treatment and follow-up of CRC patients (2000). Whichever primary screening modality is chosen, a high proportion of the population will be subjected to invasive endoscopic procedures either as a primary screening tool or secondary through work-up of screen-positives and later surveillance (Figure 3).

Complications from colonoscopy are rare. In a recent report from a screening and surveillance programme the most serious were perforations in 0.19 per 1000 and bleeding requiring hospitalisation in 1.59 per 1000 examinations (Ko et al., 2010). The generally accepted rate of perforation is less than 1 in 1000 screening colonoscopies (<0.1%), while for FS it should be less than 1 in 25 000-50 000 (Valori et al., 2010). There is considerable variation between endoscopists in their performance regarding caecal intubation and polyp detection rates and their ability to perform painless colonoscopies (Brethauer et al., 2003; Hoff et al., 2006; Seip et al., 2010). Being subjected to an endoscopist with a low detection rate for adenomas is associated with an increased risk of future CRC (Kaminski et al., 2010). Therefore, quality
assurance does matter for major endpoints of the screening service.

The Gastronet programme for improvement of colonoscopy services in Norway was established in 2003, but has since expanded to include Warszaw, Poland. Iceland and Latvia are expected to join in 2011 (www.kreftregisteret.no/gastronet). Much of the requirements in endoscopy quality assurance is incorporated in a software especially developed for CRC screening programmes and trials (Hoff et al., 2009b).

Unwanted effects of CRC screening services
Any screening programme involves screening of many for the benefit of few. Increasing the attention to un-healthy behaviour in a presumably healthy population may arouse unnecessary anxiety and time expenditure for the vast majority of the screening population. This concern finds little support in the literature of screening using FOBT, FS or colonoscopy (Lindholm et al., 1997; Wardle et al., 1999; Thiis-Evensen et al., 1999b). FOBT may cause some temporary increased anxiety (Lindholm et al., 1997), but endoscopy screening largely disclosing findings immediately for the attendee while lying on the coach does not allow time for unnecessary worry to arise (Thiis-Evensen et al., 1999b).

There is a possibility that people attending screening programmes might feel that they do not need a healthy lifestyle. There is some documentation for this regarding CRC screening (Hoff et al., 2001; Larsen et al., 2007) as well as screening for lung cancer (van der Aalst et al., 2010a). For possible screening effects on lifestyle the overall evidence is conflicting and insufficient to conclude (van der Aalst et al., 2010b), but combining screening with educational efforts on lifestyle advice seems particularly sensible for lifestyle-related diseases like CRC and lung cancer.

Eight out of ten positive FOBT screening tests are false positive for CRC, triggering unnecessary invasive investigation by colonoscopy. FS screening with tissue sampling of lesions has no false positives. Adenomatous polyps discovered at FS are easily classified into low-risk and high-risk lesions. Five percent of FS-screened individuals have high-risk lesions – the same percentage expected to test positive with iFOBT. It is, however, easier to
advocate work-up colonoscopy of 5% of FS screenees categorised as high-risk, than 5% of FOBT screenees – 80% of which are false positive.

Although endoscopy screening services may be organised separately from services for symptomatic patients, usually it will be integrated impinging on resources that should primarily serve symptomatic patients. In the USA, half of all colonoscopies are performed as part of screening services (Seeff et al., 2004). Part of the quality assurance of CRC screening should therefore be to monitor its effects on the services for symptomatic patients. On the other hand, it may be that introduction of screening may improve the service of symptomatic patients as suggested recently for mammography screening indirectly improving outcome of treatment for breast cancer by establishment of multidisciplinary teams and improved logistics developed initially within the screening programme (Kalager et al., 2010).

**Conclusion**

Many screening programmes have been implemented with the best of intentions and great conviction of taking health services into a new dimension of health-promoting preventive medicine. Quantification of the benefits and harms of screening are increasingly in demand – not least from the target population which too often appear not convinced that "there is anything in it for them" and not worth the personal effort to attend for screening. In the era of evidence-based medicine, results from well-designed randomised trials are increasingly in demand. Organised screening programmes should be considered as natural platforms for testing out new screening modalities – continuously aiming at optimising the screening service provided.

**Abbreviations**

- CRC: Colorectal cancer
- FOBT: Fecal occult blood test
  - gFOBT: Guaiac-based test for detection of occult blood in stools (fecal occult blood test)
  - iFOBT: As above, but based on immunochemical methodology to detect human occult blood only (i.e. not sensitive for intake of red meat and less sensitive to other reasons for false positive testing)
- FS: Flexible sigmoidoscopy
- IDCA: International Digestive Cancer Alliance
- NORCCAP: Norwegian Colorectal Cancer Prevention trial. A randomised trial on flexible sigmoidoscopy screening carried out in Norway 1999-2001
- NordICC: Nordic-European Initiative on Colorectal Cancer. A randomised trial on colonoscopy screening which started in 2009
- RCT: Randomised controlled trial
- TPS-I: Telemark Polyp Study no I. A two-stage randomised trial in Telemark, Norway –first using once only flexible sigmoidoscopy (1983) and then once only colonoscopy on an expanded sample of the population 13 years later (1996)
References


Epidemiology
Prostate cancer is the second most common cancer in men worldwide, with approximately 900,000 new cases diagnosed per year (14% of new cancer cases) (Ferlay et al., 2010). Subsequent to widespread testing with prostate specific antigen (PSA), a considerable increase in prostate cancer incidence has been observed in many high-resource countries (Bray et al., 2010). The most prominent increase was seen in the United States where incidence rates doubled from 1986 to 1992 (Potosky et al., 1995). There are considerable variations in the incidence between ethnic populations and countries around the world (Ferlay et al., 2010). The highest incidence rates are found in the black population of the U.S., while the lowest rates are found in populations of Asian origin (Miller et al., 1996). It has been suggested that the differences between ethnic populations may be explained by genetic differences associated with testosterone metabolism (Shibata and Whittemore, 1997), although changes in the environment and diagnostic activity are also likely contribute.

Migrant studies have shown that when people from low-incidence countries move to high-incidence areas, incidence rates increase substantially (Haenszel and Kurihara, 1968; King and Haenszel, 1973). These observations are in part explained by the “exposure” to different health care systems with different awareness to prostate-related symptoms and different levels of diagnostic activity, but are also thought to be related to alterations in life style habits such as dietary changes.

The mortality rates have begun to decline in a number of countries from the early-1990s and onwards (Bray et al., 2010; Oliver et al., 2001; Baade et al., 2009). In 2008, prostate cancer accounted for around 6% of all cancer deaths among men worldwide, with an estimated 258,000 registered deaths. Mortality rates are highest in the Caribbean and in sub-Saharan Africa, very low in Asia and intermediate in Europe and Oceania (Ferlay et al., 2010).

Survival and mortality in prostate cancer epidemiology

<table>
<thead>
<tr>
<th>Mortality rate</th>
<th>Number of deaths of a disease in a defined population over a given time period divided by the total person-time at risk during that period.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival rate</td>
<td>The percentage of men with a disease who survive a disease for a specified length of time. For example, if the 5-year survival of a cancer rate is 20%, this means that 20 out of 100 people initially diagnosed with that cancer would be alive after 5 years.</td>
</tr>
</tbody>
</table>

To distinguish mortality from survival is particularly important for the understanding of prostate cancer epidemiology. An increase in the five-year survival rates for cancer is often used to measure improvement in cancer management and health care. However, earlier detection of a cancer (i.e. caused by screening) will advance the date of diagnosis to a previous point in time. As a consequence, the estimated survival time will increase, even if there is no postponement of death. The mortality rate is not influenced by this bias (lead time bias).
In Norway an average of approximately 4000 new cases were diagnosed per year in the period 2004-2008, making prostate cancer the most common cancer diagnosed in men (30% of all new cancer cases in men) (Engholm et al., 2009). Coinciding with the increase in PSA-testing of asymptomatic men throughout the early 1990s, the incidence of prostate cancer has almost doubled in Norway (Figure 1). Currently, the life time risk of being diagnosed with prostate cancer before the age of 75 in Norway (assuming the absence of competing causes of death) is 12.5%. Prostate cancer mortality rates in Norway are among the highest in the world (Quinn and Babb, 2002), and the reason for this is unknown. An average of approximately 1050 persons died from prostate cancer per year in the period 2004-2008, which corresponds to around 20% of all cancer deaths in men. The life time risk of dying from prostate cancer before the age of 75 is approximately 1.4% (Engholm et al., 2009). Mortality from prostate cancer has decreased since 1996 (Kvåle et al., 2007) (Figure 1). The reasons for the decrease in mortality are not clear.

**Tumour biology**

Prostate cancer is a heterogeneous disease with large inter-individual variations in tumour progression rates. The largest clinical challenge is to separate aggressive from non-aggressive tumours, many of the latter ones not requiring treatment for many years. Thus, the outcome of localised prostate cancer may be favourable even without treatment (Johansson et al., 1997). This clinical experience is supported by autopsy studies which have shown that there is a high prevalence of latent and probably indolent prostate cancers that remain undetected during life (Lundberg and Berge, 1970; Guileyardo et al., 1980). Other autopsies of men from Detroit showed that the rate of latent prostate cancer increased markedly with age, with the proportion of prostate cancers detected ranging from around 40% in men aged 50-59 to around 70% in men aged 70-79 (Sakr et al., 1996). These figures are in contrast to the reported 1.4% risk of dying from prostate cancer before the age of 75 in Norway, illustrating the substantial potential for increased detection of nonlethal
tumours by extended diagnostic activities. The incidence of prostate cancer will therefore increase as a consequence of increased diagnostic activity, although many of these screen-detected tumours would never have developed into clinical relevant disease if they remained undetected. Hence, a major challenge of population-based PSA screening is to avoid detection of clinically indolent cases of prostate cancer.

The Prostate specific antigen (PSA) test
PSA is a serine protease belonging to the family of glandular kallikrein-related peptidases and the physiological role of PSA is considered to be liquefying of the seminal fluid (Lilja, 1985). It is produced in prostate epithelial glandular cells, and only a small fraction enters the circulating blood under normal circumstances. As the PSA test is prostate-specific but not cancer-specific, patients with benign enlargement of the prostate (benign prostatic hyperplasia (BPH)) may have elevations of PSA in the same range as those PSA levels that may be elevated as a result of cancer (Schröder, 2009). PSA testing for diagnosis and follow-up was introduced in the U.S. in the early 1980s, and has been increasingly used in Norway since the late 1980s. A PSA value of less than 4.0 ng/mL has traditionally been considered to be normal. However, results from the control arm in the Prostate Cancer Prevention Trial (PCPT) have shed light on some of the problems related to the use of this cut-off value for detection of Prostate cancer (Thompson et al., 2005). Today it is accepted that no cut-off value can be identified where both sensitivity and specificity of the PSA test are at completely satisfactory levels (Table 1). Importantly, a significant number of potentially aggressive cancers (with high Gleason scores) have been reported in patients with PSA values within the traditional normal range.

In order to enhance the predictive value of PSA as a tumour marker, different molecular sub-forms of PSA (free (fPSA) / total PSA (tPSA) - ratio), and PSA kinetics (PSA-velocity, PSA-doubling time) have been studied. By using the ratio of fPSA to tPSA in addition to tPSA, information can be gained as to separate men with BPH from those with prostate cancer, and the cancer detection rate increases (Roddam et al., 2005). However, as the magnitude of its effect has varied between studies and its ability to provide useful predictions of prostate cancer diagnosis may be limited, the clinical importance of %fPSA has been debated (Lilja et al., 2007).

<table>
<thead>
<tr>
<th>Any cancer vs. no cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA ng/mL</td>
</tr>
<tr>
<td>1.1</td>
</tr>
<tr>
<td>1.6</td>
</tr>
<tr>
<td>2.1</td>
</tr>
<tr>
<td>2.6</td>
</tr>
<tr>
<td>3.1</td>
</tr>
<tr>
<td>4.1</td>
</tr>
<tr>
<td>6.1</td>
</tr>
<tr>
<td>8.1</td>
</tr>
<tr>
<td>10.1</td>
</tr>
</tbody>
</table>
There is also limited evidence supporting that pre-treatment PSA kinetics provide better predictive diagnostic and prognostic information than the absolute PSA level alone (O’Brien et al., 2009; Ulmert et al., 2008; Vickers et al., 2009).

Biopsy techniques and strategies also considerably influence the risk of diagnosing prostate cancer at specific PSA values. Throughout the PSA-era the ultrasound-guided biopsy strategy has evolved. The original “sextant” biopsy technique implied six biopsy cores, containing a comparatively large amount of centrally located tissue (transition zone). By increasing the routine number of biopsies to 10-12, and directing biopsies laterally in the prostate, additional positive biopsies are found (Eichler et al., 2006).

The effectiveness of PSA-screening
Results from previous descriptive studies concerning the relation between population-based PSA testing and mortality from prostate cancer have been inconsistent. A significant reduction in prostate cancer mortality was found in Tyrol (risk ratio of 0.81, 95% confidence interval: 0.68 - 0.98) after PSA testing had been offered to all men aged 45–74 years free of charge, unlike in other parts of Austria (Oberaigner et al., 2006). Similarly, a more notable decline in mortality in the U.S. compared with the U.K. over the period 1994-2004 was observed concurrently with a high intensity of PSA-screening amongst the U.S. population (Collin et al., 2008). In contrast, another U.S. study reported a more rapid uptake of PSA testing in Seattle compared to Connecticut, but found no difference between these two states in prostate cancer-specific mortality among men aged 65 or older after 15 years of follow-up (Lu-Yao et al., 2008). A study from Canada reporting incidence and mortality changes in different health areas, found no association between the incidence levels of prostate cancer (as proxies for PSA-testing frequency) and subsequent decreases in prostate cancer mortality (Coldman et al., 2003). Case-control studies have also failed to demonstrate a consistent association between PSA screening and a reduction in the risk of death from prostate cancer (Concato et al., 2006; Weinmann et al., 2005).

The results from two randomised studies on prostate cancer screening among asymptomatic men, one from the U.S (PLCO) and one from Europe (ERSPC) have been published in 2009 (Schröder et al., 2009; Andriole et al., 2009). After a median follow-up of nine years the ERSPC reported a relative prostate cancer mortality reduction of 20% in men who were randomised to the PSA screening arm. The reduction of prostate specific mortality was 31% after adjusting for contamination and non-attendance (Roobol et al., 2009). In contrast, the PLCO study was not able to show any mortality benefits from combined screening with PSA testing and DRE during a median follow-up of 11 years. However, the PLCO trial was smaller (PLCO: 76693 participants (age 55-74 years), ERSPC: 162243 participants (age 55-69 years)) and thus less mature, despite a longer median follow-up time than the ERSPC trial. This aspect, together with the fact that 52% of the individuals in the control group had undergone a PSA test within the first five years of follow-up may have contributed to the negative findings.

One of the key findings when considering the balance between the benefits and harms of population-based prostate cancer screening is the risk of overdetection (the detection of a cancer that will not progress to clinically relevant disease during a man’s lifetime) and overtreatment (treatment of men whose prostate cancer never will threaten their lives). According to the ERSPC trial, 1410 men would need to be screened with an average of 1.7 screening visits per subject during a 9 years period in order to prevent one death from prostate cancer. Of these 1410 men about 220 men showed a positive PSA test. After further examinations 48 (the number needed to treat (NNT)) men with screen-detected prostate cancer would have to be treated, as compared to the control group, to save one life.
However, as the NNT to avoid metastatic disease in one man was 24, the absolute risk reduction may become more favourable with longer observation time. In the much smaller Göteborg randomised population-based screening study (Hugosson et al., 2010), which had a median follow-up of 14 years, most of the benefit from screening occurred after 10 years. This also indicates that the final effectiveness of population based PSA screening can only be evaluated after very long observation times. The number needed to screen in this trial (NNS) was 293, and the number needed to be diagnosed to prevent one death from prostate cancer was 12. However, even if we consider the results from the most beneficial trials such as the Göteborg study, the absolute mortality decrease is likely to be rather small. According to the data from this study, screening may reduce prostate cancer mortality from nine to four men per 1000 men at 14 years of follow-up. Further, for each prostate cancer death avoided, 11 men may be diagnosed without any beneficial prospects of life prolongation. Consequently, many men may unnecessarily be afflicted with anxiety and severe treatment related side-effects.

If restricted to selected groups, PSA screening may be more beneficial. A recently published paper indicates that the benefit of screening may be larger among men in good health (Crawford et al., 2011). In this study a reanalysis of the data from the PLCO trial was performed after stratifying the data by comorbidity. A significant decrease in the risk of prostate-cancer specific mortality was observed in those with few or no comorbidity. The NNS was 723 and the NNT was only five. Among men with several comorbidities there was a trend towards increase in prostate-specific mortality in the screening group. Selective or stratified screening may also prove to be effective in men who belong to families with increased occurrence of prostate cancer. Studies have indicated that the predictive value of PSA screening is high in BRCA mutation carriers and that the cancers detected in these men are clinically significant, supporting the rationale for screening in such men (Mitra et al., 2011). Due to on average younger age at onset of hereditary prostate cancer, and thus less age-related comorbidity, the potential benefit of early diagnosis and treatment with curative intent may increase. Yet, the known side-effects of treatment may be less acceptable for younger patients.

As the treatment of prostate cancer is afflicted with severe long-term side effects, the risk of overdetection and overtreatment should always be considered when an asymptomatic man asks for a PSA-test. Men should not be screened before they have obtained information about the potential benefits, the uncertainties and risks of PSA-testing. According to Sanda et al (Sanda et al., 2008) and Pardo et al (Pardo et al., 2010) radical prostatectomy is after 2-3 years, dependent on pre-treatment function and surgical technique, followed by sexual and urinary dysfunction in 50%-80% and 15-30% of the patients respectively. Correspondingly, the comparable figures after radiotherapy range between 30%-50% and 10%-15%. Lack of energy and reduced vitality are adverse effects in men on androgen deprivation treatment. Thus, the prevalence of the treatment-related toxicity must be balanced against an increased probability of surviving from prostate cancer. In recent years, selective delayed intervention (active surveillance) for low-risk prostate cancer has been promoted as a treatment strategy to reduce over-treatment of indolent cancers (Roemeling et al., 2007; Klotz et al., 2010). Preliminary results are promising, but longer follow-up is required before this treatment modality can be accepted for patients with highly selected tumours.

**Concluding remarks**

There is some evidence supporting a beneficial effect of screening with PSA on prostate cancer mortality. However, the crucial question whether the benefits of population–based PSA screening on mortality outweigh the physical and psychological harm caused by the test and the following treatment
is still unanswered. Improved diagnostic methods will hopefully be developed to better separate the indolent from the aggressive prostate cancer tumours in the years to come. Modifications of today’s treatments may also reduce side effects in patients undergoing treatment.

Reflecting the present knowledge about prostate cancer screening, the European Association of Urology (EAU) has formulated a position statement regarding prostate cancer screening in Europe (Abrahamsson et al., 2009) (quotation from the first paragraph): “Prostate cancer is a major health problem and one of the main causes of male cancer death. However, current published data are insufficient to recommend the adoption of population screening for prostate cancer as a public health policy because of the significant overtreatment that would result. Before screening is considered by national health authorities, the level of current opportunistic screening as well as issues of overdiagnosis, overtreatment, quality of life, cost, and cost-effectiveness should be taken into account.”
References


