PREVENTION OF CERVICAL CANCER -

The National Screening program in Norway

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Introduction

Cervical cancer is the second most common form of cancer in women in the developing world, but the incidence is generally lower in the Western part of the world. In Europe approximately 52 000 women are diagnosed each year, of which 27 000 die of the disease (21). Every day a woman gets diagnosed with cervical cancer, while almost ten women receives the diagnosis of severe pre malignant state. The disease is the second most common cause of death due to cancer among women globally and lead to ca. 190 000 deaths annually (17). In Norway a national mass examination program against cervical cancer has been in practice since 1995. The aim is to reduce prevalence and mortality while at the same time promote rational testing procedures (6).

Etiology

The Human papillomavirus, HPV, has been established as being the major carcinogen in the development of cervical cancer. Several risk factors such as other sexually transmitted diseases, sexual activity, smoking, immune suppression and diet may be important (12)

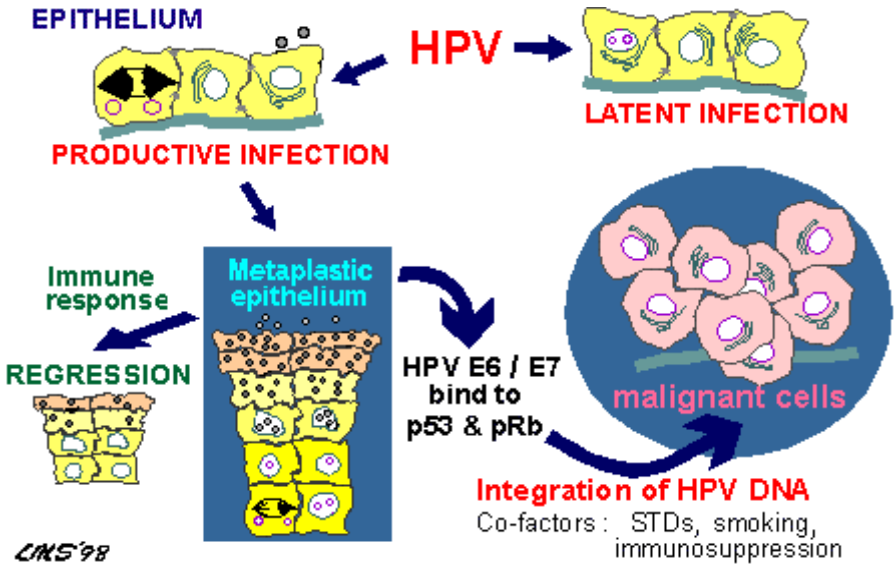
Symptoms & Signs

Many early lesions and micro invasive carcinomas are asymptomatic and are detected by cervical screening. Those with larger lesions present with postcoital bleeding, intermenstrual bleeding or postmenstrual bleeding. Some patients may complain of a profuse offensive vaginal discharge, which may be blood stained. Other symptoms, such as pain, are uncommon until a very late stage (22).

Human papillomavirus as a risk factor in carcinogenesis

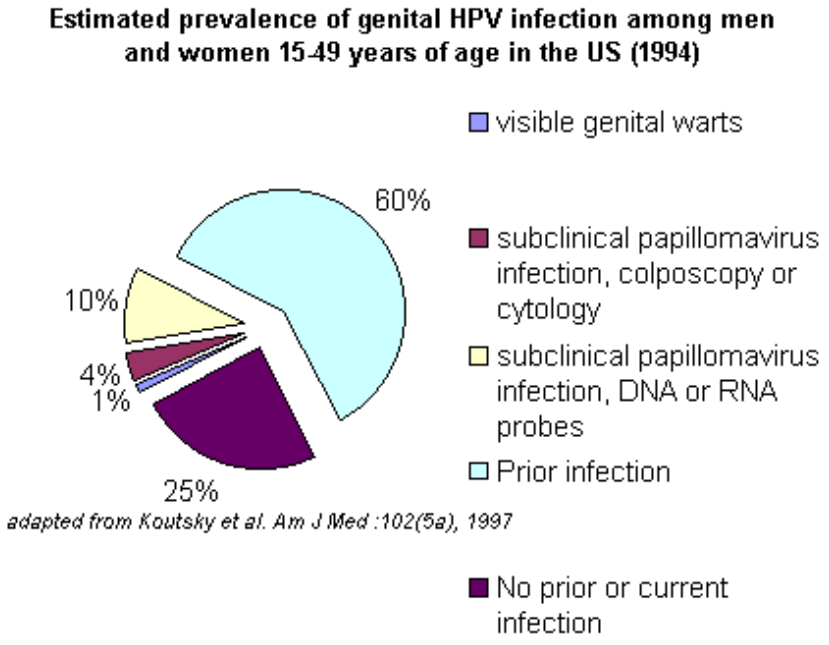
Infection of human papillomavirus (HPV) is one of the most common sexually transmitted diseases. The prevalence is thought to be increasing (12). The causal link between Human papillomavirus (HPV) and cervical neoplasia has been established through clinical, epidemiological and molecular studies during the last two decades. In 1995, HPV 16 and 18 were classified as human carcinogens (12) and in 1999, HPV 6 and 11 were included in the group of human carcinogens (20).
Infection with the human papillomavirus (HPV) is essential for the development of the first stage of cervical cancer. HPV infection is transmitted through sexual contact, and an increasing prevalence in the population may have contributed to an increasing risk for cervical cancer. Most cases of cervical cancer are squamous carcinomas, adenocarcinomas are less frequent., but human papillomavirus is found to be the causal factor for both (4).

Almost all patients with cervical carcinomas and precursor lesions are HPV-positive. HPV is a necessary, but not sufficient factor in carcinogenesis. (20) High prevalence of HPV-DNA have also been found in carcinomas of other anogenital regions; however, HPV does not seem to be important in prostate carcinogenesis. Recent studies have shown that HPV may be a risk factor in carcinogenesis in the respiratory and upper digestive tract, but its aetiological role has yet to be proved. (12)



Most of the cervical carcinomas are as mentioned above HPV positive, and it is being discussed as if HPV-negative cervix carcinomas exists at all (18). In the most extensive multinational studies which as been performed, HPV 16 alone is found in over 50% of the cases, while HPV 16, 18, 31, 33 and 45 is demonstrated in more than 80% of all cervical carcinomas. (12)

Women infected with oncogenic HPV types, have a 40-80 times higher risk for development of high grade cervical intraepithelial neoplasia (CIN II-III) (8)(20). It has been estimated that only 12-22% of infection of CIN III will progress to invasive cancer. The prevalence of HPV infection is highest among young women, 13% of women without proven cervical neoplasia have infection with oncogenic HPV types (14) According to a Dutch study of 3000 normal pap smears in women between 15-69 years, the highest prevalence of human papillomavirus was found in women 25 - 29 years of age, it was 19.6%. Prevalence was 10% in the age group 30-39 years, and 4.3% in all women above 30 years of age (24).



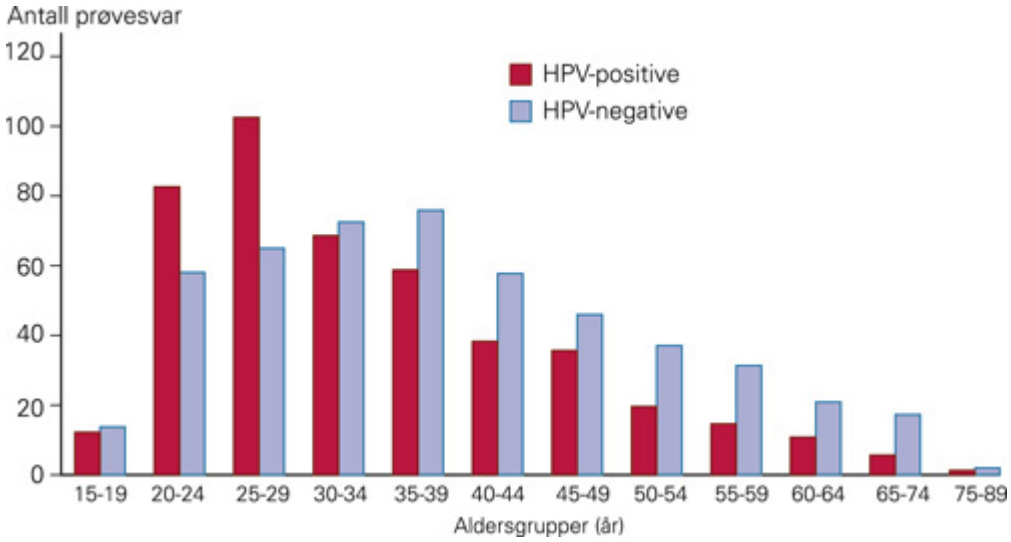


Figure 1. Prevalence of HPV infection in specific age groups in Norway (16)

Cervical cancer in Norway

The prevalence of cervical cancer has decreased in the period from 1990-1994 up until 2000-2004. Age adjusted rates decreased from 127 to 95, a decrease of 25%. In the time period between 1953-2004 the prevalence of cervical cancer was at its highest in the period between 1970-1974. After this peak period the rate has been falling, only interrupted by a slight increase in the period 1985 - 1989 and 1990 - 1994 (fig 1). This pattern one can find in all age groups (tab 1). The highest incidence rate of the disease despite the various time periods is in the age group 40-54years of age (tab 1).

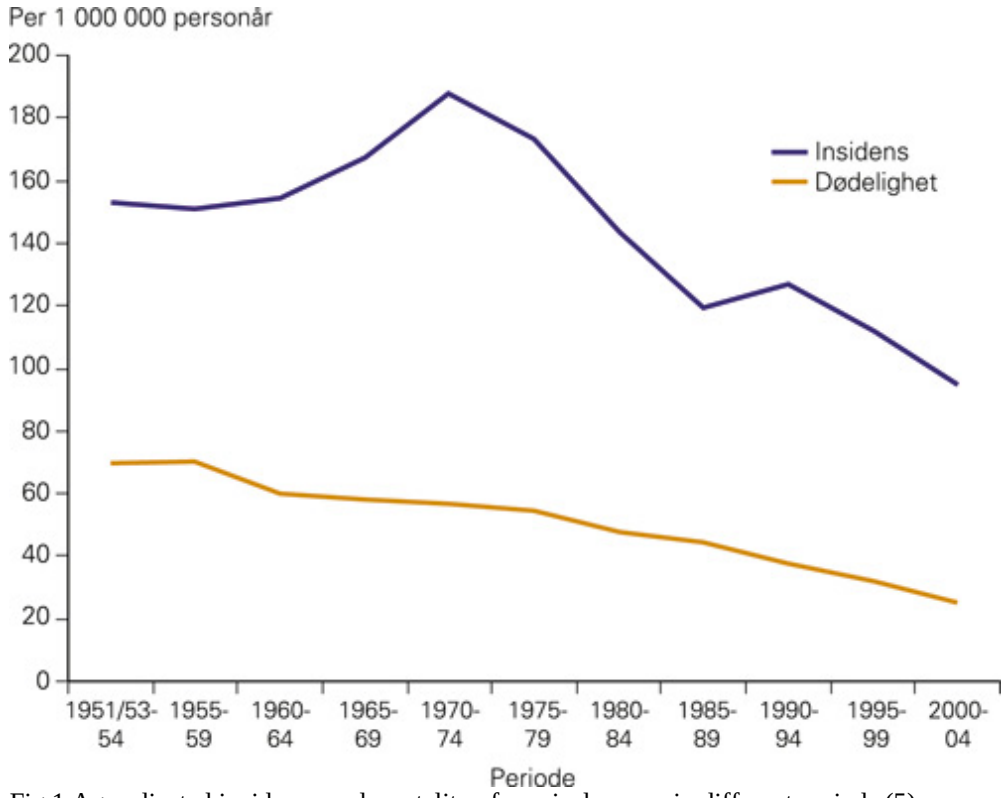


Fig.1 Age adjusted incidence and mortality of cervical cancer in different periods (5)

Tabell 1 Insidens av livmorhalskreft per 1 000 000 personår etter alder og periode

	Perioder						Prosentvis nedgang 1990–94 til 2000–04	
Alder (år)	1953–54	1970–74	1985–89	1990–94	1995–99	2000–04		95 % KI
0–19	0	0	0	0	0	0		
20–24	5	22	23	29	23	13	55	3–79
25–39	190	223	189	221	173	171	23	12–32
40–54	390	506	241	257	248	209	19	8–28
55–69	378	406	277	266	237	175	34	23–44
70–74	219	297	258	238	225	155	35	13–52
75+	259	212	222	247	188	180	27	12–40
Aldersjustert	153	188	120	127	112	95	25	20–28
Antall tilfeller	650	2 189	1 636	1 809	1 635	1 457		

Table 1. Incidence of cervical cancer per 1 000 000 person year by age and period. (5)

Most cases of cervical cancer are squamous carcinomas, adenocarcinomas are less frequent. In the period 2000 - 2004, 18 % of the cases were adenocarcinomas. From 1990 - 1994 until 2000 - 2004 the age adjusted rate for squamous carcinomas decreased from 102 to 70, a decrease of 31% while, the prevalence of adenocarcinomas increased (5). The mortality of the disease has over time had a different development than its incidence. Without interruptions there has been a clear decrease in mortality from the 1950's up until today. (Fig 1) Age adjusted mortality rates decreased from 38 to 25 between 1990-1994 and 2000-2004, a decrease of 34% (5). Between these time periods it has been observed a markedly decrease in mortality for all age groups. For all reported periods the mortality rate is greatest in the age group 70 years and above.

Tabell 3 Døde av livmorhalskreft per 1 000 000 personår etter alder og periode

	Perioder						Prosentvis nedgang fra 1990–94 til 2000–04	95 % KI
Alder (år)	1951–54	1970–74	1985–89	1990–94	1995–99	2000–04		
0–24	1	0	1	1	0	1	25	-349–87
25–39	59	31	31	23	18	14	40	7–61
40–54	162	135	76	70	62	54	23	2–40
55–69	192	177	156	127	107	70	45	31–57
70+	233	204	206	191	176	140	27	13–39
Aldersjustert	69	57	45	38	32	25	34	25–42
Antall døde	604	781	746	673	610	489		

Table 2. Death due to cervical cancer per 1 000 000 personyear according to age and period. (5)

In the time period 2000 - 2004, 215 of the 489 women who died of the disease were 70 years of age or more. In 2004, 81 women died of the disease and 267 was diagnosed with the disease. This is the lowest annual number observed in the period from where rapports exists.

Over time there are changes concerning at what stage the disease has reached when it has been diagnosed. In the period 1953 - 1954, 30% of cases were in Stage I when diagnosed, 28% were in Stage II, 26% in Stage III and 11% in Stage IV. The equivalent numbers for the period 2000-2004 were 58 %, 19 %, 11 % and 9 %. Those are great differences in time development of stage specific disease (8).

After the introduction of the national mass examination against cervical cancer the total of cytological tests have decreased from 542 666 in 1994 to 486 118 in 2004 (5).

Less than half of those 296 women who were diagnosed with cervical cancer had a pap smear performed 6 months to 4 years before the diagnosis, i.e followed the encouragement to undertake a pap smear every third year. The percentage of women who had taken a test markedly decreased with age (4).

In the ten years period after the official coordination of screening against cervical cancer started there have been a decrease in prevalence and mortality of the disease. The effect of taking a cytological test lies primarily in that pre malignant stages are discovered and treated so one avoids cancer at a later time, in less respect than that cancer is proven by pap smears (5). That means that the full effect of the screening will not be fully visible until after a certain time. Another problem present when ones want to use a number to se the effect screening is that the underlying risk factor can change over time.

By a national screening one does not have any control group to compare results with. One possibility is to compare national numbers from before the screening was started, but then one might underestimate the screening effect if the underlying risk factor increases and overestimate if it increases (19).

There are some indications that the underlying risk factor for the disease have increased the last two decades. From a peak level in 1970-1974 the prevalence of cervical cancer declined for several decades. It is natural to believe that it was due to the increasing amounts of pap smears that were done at that time and the following treatment of pre cancerous states.

Around the 1990s the declination of incidents stopped and it may seem that the potential in the unorganised screening was not extensive enough to prevent the manifestation of the underlying risk factor in observed cases (18)

The increased incidence of the disease concern mainly the Stage I of the disease, it is first in this group one will observe a increasing risk, since the time from pre cancerous stage and to the diagnosis is shorter for more advanced disease (11).

At this time one observed also an increased prevalence in other European countries

(24). In an analysis of trends according to time periods for thirteen European countries it was proven that Norway was in a group of countries where it seemed like if one in the 1990s experienced birth cohorts with increased risk was present in the age when the disease was most prevalent (9).

Since the 1950s the mortality due to cervical cancer has been decreasing. In the first decade this was due to a more favourable staging and classifications at the time of diagnosis. Even though the incidence increased, the mortality declined largely due to the demonstration of the disease before it reached an advanced stage. The decline in mortality seem to be less significantly due to improved treatment, since stage specific survival has changed relatively little over time (23)

A cytological test is not suitable to demonstrate pre cancerous stages of adenocarcinomas, which is why the trends related to time periods shows that squamous cancer is mostly affected by screening (1). The observed prevalence of adenocarcinomas may indicate that the underlying risk factor for both types is on the increase, but that observed trends for squamous carcinomas is strongly modified due to the screening (7).

Screening

A topic constantly being debated is what the optimal age for cervical screening should

be and what should the screening consist of. Until now morphological/cytological diagnostics have formed the basis for mass investigation, early diagnosis and treatment. The method is very resource demanding. New knowledge about etiology and pathogenesis has lead to studies of other markers. This includes demonstration of HPV-DNA or -RNA and markers for disturbances in the cell cycle (14). They show high sensitivity, but the specificity is temporarily too low for prediction of clinical cell changes. Due to this these screening methods are not recommend in the primary national screening program at the time.(13). The HPV testing on the other hand, is receiving a lot more attention these days as a supplement to cytological testing. The main tools for detection of cervical cancer per se is by performing a pap smear and look for cytological cell changes (14). If there's any suspicious or inconclusive findings it is proceeded by colposcopy examination. The introduction of HPV testing into the preventive program of cervical cancer is yet to be determined. By an eventual introduction of liquid based cytological investigation, HPV testing can easily be performed, directly and without a second consultation and test taking (16)

Cytological testing

The technique of cytological testing for documentation of pre malignant stages was developed in the 1950's (1). In the beginning the test was only taken on the initiative of the woman herself or her doctor. After some time the number of tests increased tremendously in Norway, from about 110 000 tests in 1970 to 512 000 tests in 1984. The incidence of the cytological testing was unevenly dispersed , some women were taking tests often while some women did not contact their doctor and were not tested at a three year interval (5)

The Cancer Directory in Norway include all women in the age between 25-59 years of age in the "Mass examination of cervical cancer" (6). Should women under 25 years be tested? It is claimed that there are as many good reasons why to include women under 25 years in the screening program as there are reasons why women under 25 years not should be included (1). This is based on an evaluation of Norwegian epidemiological data and differ than the evaluations done internationally.

The recommendations from both the IRC and WHO is based on extensive investigation about national screening programs with cervix cytological tests. The work which was published in 2005 shows that organised screening of women in the age 35-64 years leads to reduced risk of cervical cancer, but that the effect of women in the ages 25-34 is less clear (21). Documented effect of women under the age of 25 years isn't available and this screening is not recommended (3). According to a Norwegian report it is stated that there should be undertaken fewer pap smears in young women. Measures that will lead to an increased turn up of the women who usually doesn't to show up for their cervical screening examination should be prioritised instead. (2)

According to a British study, screening is most beneficial in the higher age groups and that screening in women under 25 years of age is uncertain (3). The sensitivity of the cytological test was lower in women under 25 years of age (15). Cervical cancer in women under 25 years was diagnosed after symptoms had prevailed and not by cervical cytology smears (2) The European commission agreed in 2003 that the lower age limit for undergoing cytological testing should be 20-25 years. In Norway the recommended guidelines hasn't been followed in the degree it was meant when the

outlines were constructed. A large proportion of tests taken of women below 25 years are for screening purposes. Due to this, more than 70% of women when reaching 25 years has undergone at least one cytological test, this is almost as high prevalence as in the women who are included in the mass investigation program (3). This practice is unfortunate due to several reasons. HPV infection is very frequent and in most cases spontaneous transient in women below 25 years.

The prophylactic use of early screening in women below 25 years seem to have a negative consequence amongst the younger women (1). Low grade cytological changes are mostly an expression of a ongoing HPV infection, and confirmation of cell changes will create unnecessary anxiety and uncertainty in young women. It is also proven likely that a great majority of cervical dysplasia does not progress into cancerous state and that cervical dysplasia more often regresses in younger women than in the older (8). Several studies, including studies performed in Norway has proven that conization of severe cervical dysplasia affects future pregnancies - it leads to lower average birth weight, more pre term births and a increased number of late abortions (9). Over treatment should therefore be avoided (3).

The practical sensitivity of a simple cytological test is far from 100%, one is searching in the screening to compensate for this with repeated tests in a three years interval (18). It is important to continuously work to improve the quality of the test procedures, the interpretation and follow-up of abnormal findings to get an optimal effect of the screening program

HPV testing

DNA testing for human papillomavirus (HPV) is more sensitive and less specific than cytological test regarding demonstration of pre malignant stages of cervical cancer (16). The clinical use of HPV testing in primary screening is not clarified, but a new randomised study from Sweden demonstrated that HPV testing additional to cytological testing leads to reduced prevalence of tests with pre malignant stages (CINII and CINIII) or cancer in the following test in women in their mid thirties (13)

HPV testing improves the specificity and sensitivity of cervical cytology and it can be used to clarify cases with atypical cells of undetermined significance (ASCUS) and low-grade intraepithelial neoplasia (16). HPV testing as a supplement to cytological tests which demonstrate low-grade intraepithelial neoplasia (LSIL) or atypical cells of undetermined significance (ASCUS) is recommended (13). In these women a positive test for the high risk virus indicate an increased risk for progression, while a negative test indicate decreased risk and less extensive follow up. In the near future it may also be included in the cervical cancer screening programme for women above the age of 30. Since the proportion of positive tests in young women is high (12), one need to be restrictive in testing women under the age of 30 years (1).

HPV testing cannot replace cytology, but will reduce false negative cytology and may improve the screening programme for cervical neoplasia. It has not yet been incorporated in any national cervical cancer screening program, but trials are ongoing in Scandinavia and in the Netherlands (24 The cost-effectiveness of HPV testing in screening has to be proven and whether or not it can affect the recommended screening-intervals (16).

The national screening program

The national mass examination against cervical cancer in Norway started up as a national program in 1995 after a few years with pilot projects. A base for the investigation to be put into progress was the establishment of a cytological register where all tests from the cervix taken from Norwegian women are registered. Rates are estimated per 1 000 000 person year(6)

The aim of the programme is to see decrease of 50% of the disease compared to the level in 1990 - 1994, there are no given time horizons for these objectives. The time for development from pre malignant states until disease summon that a minimum of twenty years may pass before one can observe full effect of screening on incidence and mortality of the disease. The results prove that one are approaching this goal.

The coverage of women participating in the screening program is a central factor for success in any preventive program. This has increased since the program started, primarily due to an increase in the participation of women over 50 years of age (22)

Roughly half of the women with cervical cancer in 2003 seem to have avoided to follow the recommendations of the programme.

There is reason to believe that some of these cases would have been avoided if the coverage of the program had been higher (23) On the other hand, half of the women with cancer, approximately half had a pap smear performed in a limited time period before the diagnosis (18).

The national screening program against cervical cancer has been in full activity since 1995. Women in the age groups 25-69 year of age which have not undertaken a cytological pap smear from the cervix during the last three years, is recommended through a letter to contact their general practitioner or gynaecologist to get this done (6). The goal of the screening program is to promote rationally test taking and to reduce the incidence and mortality of the disease.

Data from the Cancer Directory is used to study the development of morbidity and

mortality due to cervical cancer. The results are registered in the Cancer Directory (6).

From the period 1990-1994 until the period 2000-2004 there was a decrease in the age adjusted incidence rate per 1 000 000 personyear of cervical cancer from 127 to 95. Squamous carcinomas decreased from 102 to 72. The age adjusted mortality for cervical cancer went from 38 to 25. The number of pap smears decreased from 542 666 in 1994 to 486 118 in 2004. The number of women in the age group 25-69 years which in the previous four years undertook a test, increased from 72,4% in 1995 to 78,3% in 2004 (5).

The introduction of a national coordinated screening against cervical cancer has had a positive development for the disease and cytological testing. Continued effort is necessary to reach the goals of the ambitious programme (23).

Cervical cancer is one of the few cancers where prevalence and mortality have been decreasing the last couple of decades. It is naturally to see this in concordance with the fact that there exists a simple test which has been used in the purpose of screening. A cytological test from the cervix can lead to further investigations where one can prove premalignant states. By treating the pre malignant states, the progression to disease and death can be prevented.
The mass examination is a cooperation between the Ministry of health and care services and the Directory for Health and Social affairs, Norwegian Institute of Public health, the pathology and microbiology departments in the country, doctors and the Cancer directory (18).

The goal of the programme is as mentioned above that the amount of cytological tests should not exceed the 1994 level (542 666 tests) and that the coverage in the age group 25-69 years shall be at least 80%. The goal also includes that age adjusted incidence rate and mortality rate of the disease is reduced by 50% compared to the period 1990-1994 (5). Statistics over the prevalence and mortality of cervical cancer are available through 2004.
Numbers of prevalence and mortality are taken from the Cancer Directory.
The register has since 1953 undertaken the responsibility of the national registration of cancer incidences. The registration is based on reports from doctors, pathology

departments and other hospital departments (6). The national programme collaborates with Statistic Norway, which stands for the central health register according to the health register legislation (18)

The division of cervical cancer regards clinical stages and follows the FIGO classification (5). Cervical cancer is staged by the International Federation of Gynaecology and Obstetrics (FIGO) staging system, which is based on clinical examination, rather than surgical findings. It allows only the following diagnostic tests to be used in determining the stage: palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and X-ray examination of the lungs and skeleton, and cervical conization.

The TNM staging system for cervical cancer is analogous to the FIGO stage.

- Stage 0 - full-thickness involvement of the epithelium without invasion into the stroma (carcinoma in situ)

- Stage I - limited to the cervix
    - IA - diagnosed only by microscopy; no visible lesions
        - IA1 - stromal invasion less than 3 mm in depth and 7 mm or less in horizontal spread
        - IA2 - stromal invasion between 3 and 5 mm with horizontal spread of 7 mm or less
    - IB - visible lesion or a microscopic lesion with more than 5 mm of depth or horizontal spread of more than 7 mm
        - IB1 - visible lesion 4 cm or less in greatest dimension
        - IB2 - visible lesion more than 4 cm
- Stage II - invades beyond cervix
    - IIA - without parametrial invasion, but involve upper 2/3 of vagina
    - IIB - with parametrial invasion
- Stage III - extends to pelvic wall or lower third of the vagina
    - IIIA - involves lower third of vagina
    - IIIB - extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney

In other countries one had organized the pap smear testing in a system and taken advantage of this in officially organized systems of screening earlier than Norway. It proved that in some of the countries where one had a organized system regarding screening that they achieved a greater decrease in the prevalence of cervical cancer compared to Norway (23). It was claimed that organized testing could be beneficial and used more effective as an aid against the disease (18)

Pilot studies performed in Norway, such as the Østfold investigation and the Tromsø investigation, indicated that screening is effective as a measure for combating the disease (5). This acknowledgment was not used in Norway such as was done in many other countries. Finland, Island and Sweden introduced national screening programmes already in the 1960s, while Denmark and Norway didn't develop such a programme until decades later.

In countries where the screening programme has been evaluated, one has observed equal tendencies; firstly there has been registered an increased frequency, then a declination and thereafter a fall in mortality. This was also observed in the Nordic countries. Those countries who introduced the national screening program early, had an earlier decline in mortality than Denmark and Norway (25).

It is claimed that a good organized screening program can reduce the prevalence of cervical cancer by 80%.(10). One does not know the specific effect of today's programme, since one can not know what the incidence would have been without the programme (5). The incidence of cervical cancer in the period between 2000 - 2004 was approximately fifty percent of the incidence in 1970 - 1974. One assumes that the underlying risk factor is greater today than previously, which predicts that the absolute effect of the programme is more than 50% (23).

The conditions in neighbouring countries such as Sweden and Finland indicate that it is feasible to achieve the goals set for the programme. The prevalence of cervical cancer in these countries are at a level which includes a fulfilment of the Norwegian goal (24).

Improved health awareness and education about symptoms and a lower threshold for patients to contact a doctor in case of symptoms in the genital area can also be a reason for the decreased mortality due to cervical cancer (11).

It is positive to observe that the mass examination against cervical cancer seem to be effective. There are still room for improvement when it comes to the coverage of the screening, today 78% of women are screened. In comparison, the coverage varies tremendously in Europe from 27% in Spain to 93% in Finland. (21)

HPV vaccine

Through work that was initiated in the mid 1980s, the vaccine was developed, in parallel, by researchers at Georgetown University Medical Centre, the University of Rochester University in Australia, and the U.S. National Cancer Institute (27) .In 2006, the U.S Food and Drug Administration approved the first preventive HPV vaccine, marketed by Merck & Co under the trade name Gardasil. According to Merck press release (28), in the second quarter 2007, it had been approved in 80 countries, many under fast-track or expedited review. Early in 2007, GlaxoSmithKline filed for approval in the United States for a similar preventive HPV vaccine, known as Cervarix in the European Union. GlaxoSmithKline filed the application for approval in March 2006. In May 2007 this vaccine was licensed in Norway.

Merck & Co has developed a vaccine against four strains of HPV (6,11,16,18), called Gardasil. It is now on the market after receiving approval from the US Food and Drug Administration in June, 2007 (26). Gardasil is targeted at girls and women of age 9 to 26 because the vaccine only works if given before infection occurs; therefore, public health workers are targeting girls before their sexual debut. The use of the vaccine in men to prevent genital warts and interrupt transmission to women is initially considered only a secondary market. The high cost of this vaccine has been a cause for concern. Gardasil has also been approved in the EU (29) GlaxoSmithKline has developed a vaccine called Cervarix which has been shown to be 100% effective in preventing HPV strains 16 and 18 and is 100% effective for more than four years (29). These strains together cause about 70% of cervical cancer cases.

There is reason to be optimistic concerning the introduction of vaccination of young girls against certain HPV types which are the cause to pre malignant stages of cervical cancer. This may be the great breakthrough in the prevention of cervical cancer (13).

In several European countries, such as Sweden, Denmark, Finland and the Netherlands the HPV vaccine has been integrated in their national vaccine programme. It will be available for all girls in the age 11-16 years in 2009 (30).

The background are studies performed on more than 30 000 vaccinated, all without

serious complications. (5) More than 2 000 of the vaccinated girls were Norwegian. The sceptics towards the HPV vaccine stress that it is not proven that the vaccine really reduces the total number of cancer incidences nor the mortality related to the disease. (13)(4). It is also not clear how long the vaccine is protective and to which extent it also protects against other oncogenic HPV-types which is not included in the vaccine. Randomised studies to prove the effect on cancer prevalence and survival will be difficult to carry out, due to ethical reasons. A cost effective study from Norwegian Knowledge Centre for Health Services suggests that vaccination against HPV type 16 and 18 can be a cost effective strategy to reduce the incidence of new cases of cervical cancer and mortality in Norway (5)

The question is who will be benefiting of the doubt and at what cost. By adopting a waiting attitude one risk to lose time by introducing a preventive measure too late to fight a serious cancer disease. The potential for a HPV vaccine is probably greater in a developing country with a high prevalence of cervical cancer, less developed health care and a minimal feasibility to carry out a screening programme.
Even if one introduce the HPV vaccine in the national vaccination programme today, this will have to occur parallel to a well functioning screening programme many years ahead.

In Norway a well functioning screening program for cervical cancer make it possible to follow the effect of HPV vaccination on the prevalence of cervical cancer.

The Norwegian Gynaecological Society and The Norwegian Institute for Public Health are promoting the introduction of the HPV vaccine into the national vaccination programme. Their recommendation is that the vaccine is introduced into the programme and offered to girls 11-12 years old and that girls who are now 12-16 years old should be offered the vaccine. Today girls need to get a prescription for the vaccine from their general practitioner and three doses cost a total of 3700 Norwegian crowns (approx 460 Euros).

The Cancer Directory

The main task of The Cancer Directory of Norway is to register, research and inform the population about cancer. From 2002 the Cancer Directory is one of the leading and most central health registers according to the health register legislation. The operation is controlled by its own regulations. This also include the activity in investigation programmes for early diagnosis of cervical cancer, among then the mass examination against cervical cancer.
One specialized division of the Cancer Directory has the responsibility for prevention, among that against cervical cancer through the national program ”Mass examination against cervical cancer” ("Masseundersøkelsen mot livmorhalskreft") which involves women in t he age group 25-69 years of age. (6).

All pap smears taken are registered in a unique registrar. This registrar is subordinated by strict demands regarding measures to protect the rights of the individual, and all results are treated highly confidential. (19) Women can reserve themselves against registration of name and personal identification number if their pap smears are normal. Women who have undergone a hysterectomy shall not participate in the program, and the doctors performing the pap smears are obliged to inform the patient about her right to reserve herself from participating in the program.

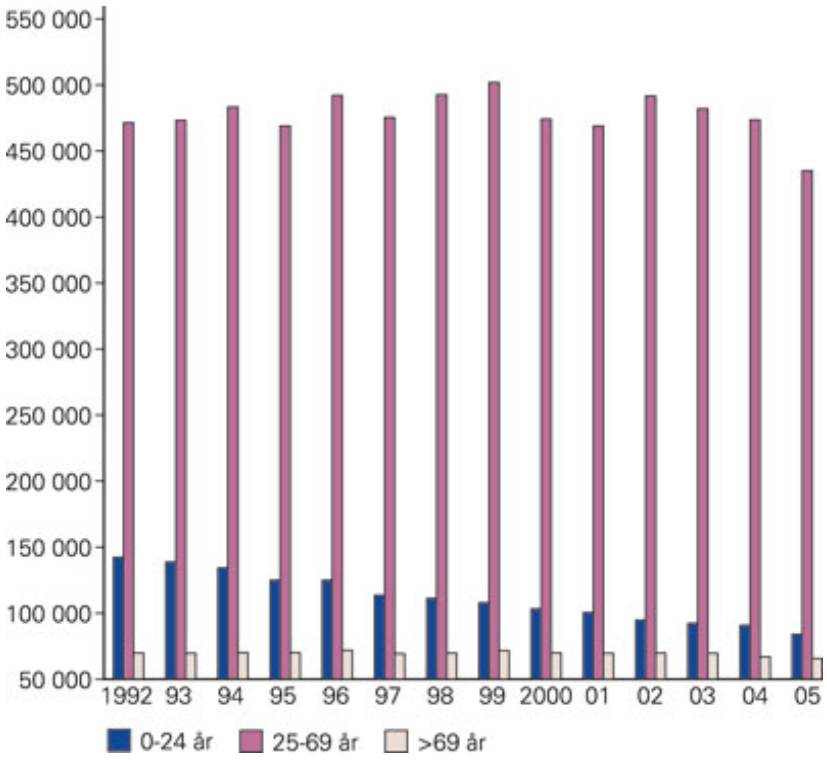


Fig.2 Investigation volume in (25-69 years) and outside (<24 and >70years) of the national Mass investigation against screening programme cervical cancer (5)

The Cancer Directory distributes six different invitation letters. (6)

1. Information letter enclosed with a brochure to all female residents living in Norway the year they turn 25 years.
2. Remind women to attend their GP's or gynaecologist to have the pap smear performed when three years have lapsed since their last smear - all women between 26 and 69 years.
3. Another reminder one year letter to those women who still have not taken the test.
4. A recommendation of control testing to the women who have taken a test of poor technical quality.
5. A recommendation to undergo a control pap smear test in those who have shown slight cell changes.
6.A recommendation of more extensive investigation to those who have not undertaken the recommended control tests where this have previously been recommended.

Research

Research shows that prevention is effective (6)(7). The findings from the program organized by the Cancer Directory are important in the development of research which will conversely improve prevention and the program.

The research can be divided into the following main categories:
1. Measures to improve the patient coverage of the investigation
2. Improve the guidelines and recommendations according to the different pap smear results.
3. Try out new technology/tests

Use of resources.

Cervical cancer prevalence is very rare in women below 25 years of age (average incidence of 3 cases per year) and rarely in the group under 30 years. (1)
In a majority of these cases where cervical cancer is diagnosed it is being diagnosed in

women belonging to the higher age groups. Many of these women do not participate in the mass examination programme (8) A more intelligent use of the available resources regarding prevention of cervical cancer will be to encourage those who do not meet for the control appointments and tone down the importance of screening amongst young women (1). The guidelines appointed from the Cancer Directory should be followed. It is encouraged to take as few cytological test in women under 25 years of age as possible (3).

It is demonstrated that the disease itself does not get eliminated even with a well functioning screening program

Conclusion

It is likely that a coordinated screening program contributes to a reduced prevalence and mortality of cervical cancer. It is certain that the screening program has been an important factor regarding the positive development.

In the ten year period after the introduction of the national screening programme there has been a decrease in mortality of cervical cancer. It has a diagnostic value to compare results from HPV testing with the cytological findings
HPV test and cytological testing demonstrate more high grade lesions than cytological testing alone and proves to be induce more confidence in excluding such a diagnosis.

Improved test taking and new vaccines against human papillomavirus (HPV) can give an additional profit. The introduction of an effective HPV vaccine will on a long term basis become an important part regarding prevention of cervical cancer. Despite an effective vaccine one will for decades to come be dependent on prevention of cervical cancer by means of screening.

It must continuously be emphasised to improve the effectiveness of the prevention.

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