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Cervical cancer screening in Sweden

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Abstract

Organised cervical cancer screening was implemented in Sweden in the mid-1960s. A marked decline in cervical cancer incidence could be attributed to the time-point of start of screening. Squamous cell carcinoma has declined by 60%, whereas adenocarcinoma has increased. About 950 000 papanicolaou (Pap) smears are taken annually. Only 31% of the smears taken in the organised screening programme. As of 1998, the screening guidelines are 3-yearly tests between 23 and 50 years of age and 5-yearly tests between 50 and 60 years of age. The article reviews the screening practise in Sweden, the current efforts to improve the quality of the screening programme, as well as the ongoing randomised evaluations of organised primary screening for cervical human papilloma virus (HPV) infection.

Keywords: Sweden; Cervical cancer screening; Organised; Opportunistic; Human papilloma virus

1. Introduction

Organised cervical screening was first implemented in Sweden in the mid-1960s. During 1959–1963 the age-standardised incidence of cervical cancer in Sweden was 20.6/100 000. Subsequent to the introduction of organised screening, there has been a regular decline and during 1989–1993 the incidence was 10.1/100 000. The entire reduction occurred for squamous cell cancers (incidence 1959–1963: 18.9; in 1989–1993: 7.6, a 60% decrease), whereas cervical adenocarcinoma has been increasing in incidence (from 0.9 in 1959–1963 to 2.0 in 1989–1993). A small proportion of cervical cancers of other types (e.g. adenosquamous cancers and clear cell cancers) that is included in the total figures has had an essentially constant incidence over the past decades. The incidence reduction in squamous cell carcinoma has been strongest in the age groups targeted for screening.

The healthcare in Sweden is organised regionally in each county. During the past three decades 26 counties have been defined in Sweden. A few of these counties also have regional screening organisations, thus there have been 30 different autonomous regional screening organisations in Sweden. The different counties implemented organised screening a few years apart and chose different target age groups and screening intervals. This has enabled the proportion of cervical screening mortality reduction that is attributable to organised screening to be estimated as 53% [1].

2. Population and methods

The Swedish National Board of Health and Welfare (SoS) has the national responsibility for the health of the Swedish population and issues national guidelines for cervical cancer screening. In the guidelines that were issued in 1985, it was recommended that all women between 20 and 59 years of age should be screened every third year. The different counties have the responsibility for the implementation and establishment of management guidelines. It was also stated that quality assurance in terms of smear usage records should be maintained and registry linkages with cancer registries be set up.

In 1995–1997, a new working group of the SoS made an inventory of how screening was actually being performed in Sweden. The results were recently published together with new national guidelines of cervical cancer screening [2].

The actual screening programmes implemented were found to deviate somewhat from the national guidelines Table 1.

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The number of smears per lifetime of the woman was also calculated. This varied from 5 smears/life to 17 smears/life, with the majority of counties (16/26) offering 11–14 smears/life.

The total amount of organised and opportunistically taken smears was on file for 24/26 counties, with one county not keeping track of the reason for smear taking and one county (the small island of Gotland in the Baltic sea with a total population of 50 000) having kept no records at all.

In 1994, these counties took a total of 948 032 smears, 291 580 (31%) in organised screening and 656 452 (69%) taken opportunistically. The figure for opportunistic smears includes smears taken during follow-up of abnormal smears (also as a result of follow-up of abnormal smears taken in organised screening) and indicated smears, i.e. smears taken as a result of symptoms or other reasons to suspect cancer. Indicated smears and follow-up smears are estimated to constitute approximately 140 000 of the non-organised smears.

For the entire country of Sweden, it is estimated that approximately 950 000 smears are taken annually.

2.1. Local organisation and screening practices

In most counties, a regional cervical cancer screening working group is appointed. The organisation itself and issuing of invitations is commonly organised by a major local cytology laboratory. In some counties (such as Stockholm) the regional Oncologic Centre is organising the programme. In several counties, it is not clear who has the responsibility.

2.2. Identification of the target population

The population registry is used. The personal identification number (PIN) in the population registry is in Sweden required for a variety of purposes, including changing of domicile address and receiving social benefits and healthcare. Screening registries, cancer registries, pathology and cytology registries are all based on the PIN. Non-eligible women are women without a uterus, women who decline participation and in most counties also women who have recently had an opportunistic smear (see below).

Table 1
Organised screening in Sweden (n = number of counties out of the total of 26 counties in Sweden)

	n
Age to start screening (years of age)	
20–21	16
25–26	6
30	4
Age to stop screening (years of age)	
50–51	4
54	1
59–60	21
Screening interval (years)	
Both 2 and 3	2
3	13
Both 3 and 4	1
4	10

Smear taking is in Sweden performed by trained midwives at the local Maternity Care centres. Utensils and quality control procedures are independently decided in each county. For example, Stockholm is taking smears with the original spatula and cotton-tipped pin procedure, most counties (including Malmö and Uppsala) are using cytobrushes, whereas a few counties, such as Västerbotten, are using a paint-brush type of cervical brush (Cervex^{TM}).

The proportion of smears taken within the organised programme varies drastically between the different counties, from 3% in the city of Malmö to 62% in the rural county of Jämtland. In general, the proportion of smears taken within the organised programme is inversely proportional to the availability of practitioners in gynaecology, with rural areas having a high proportion of organised smears and major cities where practitioners in gynaecology are readily available having the lowest proportion. The three regions with the lowest degree of organisational screening are three of Sweden's four major cities (Malmö, Gothenburg and Uppsala). The capital itself (Stockholm), which is Sweden's biggest city, is an exception, in all likelihood due to its exemplary well organised screening programme.

The average number of smears taken per year per woman aged 20–60 years is 0.41 for the entire country. This measure is a reflection of the screening intensity in an area, although it should be emphasised that it says nothing about coverage. There is again enormous variation between counties, from the city of Malmö with 0.69 down to 0.22 in a rural county.

The attendance rate in organised screening also varies greatly. Three counties have attendance rates over 80%, e.g. the Northern Sweden county of Västerbotten with a $>85\%$ attendance rate. The worst region is again the city of Malmö with an attendance rate of 20–30%. Two counties had no records of attendance rates and an exact average attendance rate for the entire country is therefore not available. However, most counties have an attendance rate of 50–70%.

2.3. Sorting out

'Sorting out' is a procedure that is recommended in the National Guidelines. The procedure involves a registry linkage of the population registry with the cytology registries in the region to find out if an eligible woman has recently had a smear taken spontaneously. In the Stockholm county, all cytology laboratories (both private

and county-owned) provide data files with analysed smears to the Oncology Centre. All women who had a smear taken in the past 18 months are sorted out and are not invited for screening. Most counties practise sorting out, but it appears that the cytology registries are not of sufficient quality to allow reliable sorting out in some regions. Sorting out affects the attendance rates and comparison of attendance rates between counties with and without sorting out before invitation may be misleading.

2.4. Coverage

No single county in Sweden has calculated population coverage [2]. It should be noted that population coverage and attendance rates may be very different in regions where a large proportion of the population is taking smears opportunistically. This phenomenon is best exemplified by the situation in the city of Malmö, where the very high smear usage (0.69 smears/woman/year) in spite of low attendance rates indicates that a substantial proportion of the population is having annual smears taken by private gynaecological practitioners.

An estimation of coverage can of course be obtained by combining the sorting out rate and the attendance rate. For example, in Malmö 76% of the eligible women in the population registry are sorted out because of having had a recent opportunistic smear. If 25% of the invited women are attending, the population coverage in Malmö is approximately 82%.

2.5. Action taken if no attendance

Nine counties send a new invitation immediately if an invited woman does not show up for screening. In the county of Västerbotten, all non-attending women will receive a new invitation with a new time and date for screening reserved for them within 14 days of the non-attended appointment. No published data are currently available on how many counties will include non-attending women in the next years' invitation such that the non-attending women will receive a new invitation every year. This is practised in the counties in the Swedish human papilloma virus (HPV) screening trial (e.g. Västerbotten will both send the immediate reminder within 14 days and transfer women who do not attend their second appointment to next years' age group due for invitation, thus never-attending women will receive two invitations every year), but there may exist counties that do not send out a new invitation until the next screening interval.

2.6. Cost for the woman

Organised screening was free of charge only in 5/26 counties. The cost for the woman varied from £5.95 to £14.88 in the different counties. In addition, in some regions, opportunistic screening carries a fee for the woman, but in general opportunistic screening is free of charge for the woman or has a lower cost for the woman than participation in organised screening.

The disadvantages of this practice are that it both promotes opportunistic screening and sub-optimal use of resources and may also result in less affluent women (a particularly relevant target group for screening) not having a smear test taken due to the high cost. This fact has been pointed out repeatedly, but to no avail.

2.7. Response to the woman

In most counties all women are informed by letter if the smear is normal, but six counties do not inform women about normal results. In all counties, results of abnormal smears are communicated to the local gynaecology clinic.

2.8. Screening results

There are huge variations between counties in the proportion of abnormal smears. The proportion of smears with the diagnoses cervical intra-epithelial neoplasia I (CINI), CINII, CINIII or suspect malignant smears varies from 0.3 to 4.4%. Counties with high and low proportions of abnormal smears are distributed haphazardly over the country, suggesting that the difference is mainly due to different diagnostic practises. Not all counties keep records, but data for approximately 80% of all smears taken during 1994, a total of 760 138 smears, have been recorded. The national figures were: CINI: 1.86%, CINII: 0.49%, CINIII: 0.27% and suspect malignant: 0.05% (altogether: 2.67%).

Out of the 760 138 smears with registered diagnoses, data on whether they were taken in an organised programme were available for 647 927 smears. Of these, 39% were organised smears and had a proportion of dysplastic (CINI, CINII, CINIII or suspect malignant) smears of 1.47%. Among the opportunistic smears, 3.01% were dysplastic.

2.9. Treatment and follow-up

In addition, treatment modalities differ greatly between counties both with regard to the use of destruction or resection, as well as to which equipment is used (cold knife, laser, cryotherapy, loop diathermy). All 30 screening organisers in Sweden stated that local guidelines for treatment and follow-up existed, but only 13/30 organisers were able to provide a copy of the guidelines on request from the National Board of Health and Welfare.

2.10. Cost efficiency

Estimation of the cost per smear by the counties themselves varied from £1.79 to £47.60, indicating that the true cost is difficult to estimate. A thorough estimation of all costs based on a representative county (cost per smear = £14.76) arrived at the estimate that each life saved by the screening programme costs approximately £59.524 [2]. This estimate did not take into account the savings due to less costs for cancer treatment and terminal care. Thus, a solid cost–benefit analysis for Sweden is still lacking.

A thorough cost–benefit analysis has been published for the neighbouring country of Finland [3]. In that analysis, the cost of the screening programme was less than the savings in cancer treatment and care.

2.11. New National Guidelines for Sweden

As of 1998, the major selected points of the National Guidelines for Sweden are [2]:

- Screening should be done at 3-yearly intervals in the age groups 23–50 years and at 5-yearly intervals between 50 and 60 years of age.
- A national working group should be instituted with responsibility for overseeing the programme at the national level.
- Each county should have one responsible person appointed for carrying out the regional screening programme.
- All cytology results should be registered.
- Coverage should be analysed continuously and should be maintained at $>85\%$ during a screening interval and at $>90\%$ during a time of a screening interval plus 2 years.
- The proportion of invitations returned because of a change of domicile or death should be continuously monitored and kept below 3%.
- Reminders should be sent in cases of non-attendance and in cases of no response to the reminder annual invitations should be mailed.
- A national annual report should be published.
- When a woman develops cervical cancer, there should be an audit to investigate whether the cancer is attributable to deficits in the screening programme.
- Forceful attempts should be made to inform all parties involved that smear taking in excess of the recommended intervals is not motivated.

2.12. Pilot project Sweden

The Europe Against Cancer Pilot project Sweden is a population-based randomised trial of screening for HPV infection within an organised cervical cancer screening programme. It is well documented that HPV testing of cytologically normal women and subsequent referral to colposcopy can result in the detection of high-grade lesions, missed by cytology [4]. These results can either mean that cytology plus HPV testing is a more effective screening test or that overdiagnosis of regressive lesions that are not true cancer precursors occurs.

If HPV testing is a more effective cervical screening test, the expected excess diagnosis of CIN should be followed by a corresponding decrease in the amount of CIN diagnosed in subsequent cytological screening rounds.

The age group targeted for the trial is 32–38-year-old women. This is chosen because maximal cost-effectiveness of a new test occurs when comparing no test to one lifetime test. Both the decreasing prevalence of HPV infection with age and the increasing incidence in cervical cancer in the age groups immediately before 40 years of age indicate that the ages 32–38 years of age would be the optimal age group for a single lifetime HPV test. Modelling has indicated that primary HPV testing can be more cost-effective and have better cancer protective effect than cytology only, provided that the protective effect of a negative test lasts longer for an HPV test than for a Papanicolaou (Pap) smear [5]. Randomised trials with prolonged follow-up are necessary for this evaluation. The trial is sized to enrol 10 000 women, which has an 80% power to detect a 50% reduction of CINII, CINIII and suspect malignant smears in the next cytological screening round of previously HPV-screened women. The trial started enrolment in May 1997 and by May 1998 approximately 6000 women were enrolled.

Four Swedish counties are participating in the trial, chosen mostly because there was a long-standing scientific experience of HPV research in these counties. The Stockholm and Västerbotten counties are running some of the best organised programmes in the country. Malmö and Uppsala are among the three worst programmes in the country in terms of poor attendance rates, they have a strong local expertise with genuine will to improve this situation. It appears that several of the actions that were necessary for the HPV screening trial, such as quality control measures of diagnoses and registries, as well as public relations efforts have had benefits also for the regular cytological screening programme. For instance, following a substantial press and regional TV coverage on the HPV screening trial, the amount of smears taken in organised screening in Uppsala county increased by 2.11-fold from 1997 to 1998 with a corresponding decrease in spontaneous smears.

Following the explicit wish of Europe Against Cancer, pilot project Sweden was extended to also include two other EU countries, Holland (J.M.M. Walboomers and C.J.L.M. Meijer) and Finland (M. Hakama). The

funds have covered the expenses required for the international collaborative dimension. As a result of the Europe Against Cancer grant, the Swedish HPV screening trial has changed the HPV test intended to be used in favour of a more simple and (as determined by extensive international interlaboratory evaluation) equally well performing polymerase chain reaction (PCR) test [6] as the nested PCR test was originally intended to be used [7]. The HPV testing methodology will now be exactly identical in the Swedish and in the upcoming Dutch HPV screening trial. In addition, the trial protocols themselves are identical, which should enable future meta-analysis of the results. A HPV screening trial is now also being planned in Finland, with a similar study design and HPV testing methodology.

To summarise, the Swedish primary HPV screening trial is one of the first randomised trials of primary HPV screening to actually start enrolment. An anticipated side-effect of the trial, that has already been seen, is that scientific interest in cervical cancer screening has increased in Sweden.

3. Discussion

The screening programme in Sweden is heterogeneous in quality. The new national guidelines seek to remedy some of the major shortcomings. In particular, the suggestion of a national working group responsible for overseeing the programme could have a major impact on the quality of cervical cancer screening in Sweden. Historically, there has, however, been limited compliance with the national guidelines by the different counties and it remains to be seen whether the new guidelines will actually result in an improvement in cervical cancer screening practices in Sweden.

A major frontier of debate in Sweden presently is whether organised or disorganised screening should be favoured and there is, therefore, some disappointment that the new guidelines did not recommend actions to specifically reduce the amount of disorganised screening. Some of the scientific articles published from Sweden should be seen in light of this debate. One article compared organised and disorganised screening in terms of amount of dysplasias detected per smear and found disorganised screening to be more 'efficient' [8]. However, the purpose of the programme is not to detect as many dysplasias as possible, but to achieve mortality reduction in cervical cancer. A valid study design to answer this question is for example the comparison of screening intervals and target groups in organised screening and mortality reduction by county, where most of the reduction has been found to be attributable to organised screening [1]. Case–control studies of the protective effect against cervical cancer mortality by organised and disorganised screening are also informative [9], but such studies have unfortunately not been carried out.

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References

1. Mählck CG, Jonsson H, Lenner P. Pap smear screening and changes in cervical cancer mortality in Sweden. *Int J Gynecol Obstet* 1994, **44**, 267–272.
2. SoS, Gynekologisk Cellprovskontroll. Förslag till screeningprogram. SoS-Rapport. Stockholm, Sweden, The Swedish National Board of Health and Welfare (SoS), 1998.
3. Hristova L, Hakama M. Effect of screening for cancer in the Nordic countries on deaths, cost and quality of life up to the year 2017. *Acta Oncol* 1997, **36**, 1–60.
4. Cuzick J, Szarewski A, Terry G, *et al*. Human papillomavirus testing in primary cervical screening. *Lancet* 1995, **345**, 1533–1536.
5. van Ballegooijen M, van Marle ME, Warmerdam PG, Meijer CJLM, Walboomeres JMM, Habbema JDF. Present evidence on the value of HPV testing for cervical cancer screening. A model-based exploration of (cost)-effectiveness. *Br J Cancer* 1997, **76**, 651–657.
6. Jacobs MV, Snijders PJ, van den Brule AJ, Helmerhorst TJ, Meijer CJ, Walboomers JMM. A general primer GP5+/GP6+-mediated PCR-enzyme immunoassay method for rapid detection of 14 high risk and 6 low risk human papillomavirus types in cervical scrapings. *J Clin Microbiol* 1997, **35**, 791–795.
7. Evander M, Edlund K, Boden E, *et al*. Comparison of a one-step and a two-step polymerase chain reaction with degenerate general primers in a population-based study of human papillomavirus infection in young Swedish women. *J Clin Microbiol* 1992, **30**, 987–992.
8. Gustafsson L, Spare'n P, Gustafsson M, Wilander E, Bergström R, Adami HO. Efficiency of organized and opportunistic cytological screening for cancer *in situ* of the cervix. *Br J Cancer* 1995, **72**, 498–505.
9. Nieminen P, Kallio M, Antilla A, Hakama M. Organised vs spontaneous Pap-smear screening for cervical cancer: a case–control study. *Intl J Cancer* 1999, **83**, 55–58.