AOGS
ACTA Obstetricia et Gynecologica Scandinavica

AOGS MAIN RESEARCH ARTICLE

Projected cost-effectiveness of repeat high-risk human papillomavirus testing using self-collected vaginal samples in the Swedish cervical cancer screening program

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Key words
Cervical cancer, cost-effectiveness, human papillomavirus (HPV), screening, self-sampling

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Conflict of interest
We have no conflicts of interest regarding any products mentioned or financial or personal relationships that might bias our work.

Please cite this article as: Östensson E, Hellström A-C, Hellman K, Gustavsson I, Gyllensten U, Wilander E, Zethraeus N, Andersson S. Projected cost-effectiveness of repeat high-risk human papillomavirus testing using self-collected vaginal samples in the Swedish cervical cancer screening program. Acta Obstet Gynecol Scand 2013; 92: 830–840.

Received: 20 December 2012
Accepted: 19 March 2013

DOI: 10.1111/aogs.12143

Abstract

Background. Human papillomavirus (HPV) testing is not currently used in primary cervical cancer screening in Sweden, and corresponding cost-effectiveness is unclear. *Objective.* From a societal perspective, to evaluate the cost-effectiveness of high-risk (HR)-HPV testing using self-collected vaginal samples. *Design.* A cost-effectiveness analysis. *Setting.* The Swedish organized cervical cancer screening program. *Methods.* We constructed a model to simulate the natural history of cervical cancer using Swedish data on cervical cancer risk. For the base-case analysis we evaluated two screening strategies with different screening intervals: (i) cytology screening throughout the woman's lifetime (i.e. "conventional cytology strategy") and (ii) conventional cytology screening until age 35 years, followed by HR-HPV testing using self-collected vaginal samples in women aged $\geq$ 35 years (i.e. "combination strategy"). Sensitivity analyses were performed, varying model parameters over a significant range of values to identify cost-effective screening strategies. *Main outcome measures.* Average lifetime cost, discounted and undiscounted life-years gained, reduction in cervical cancer risk, incremental cost-effectiveness ratios with and without the cost of added life-years. *Results.* Depending on screening interval, the incremental cost-effectiveness ratios for the combination strategy ranged from €43 000 to €180 000 per life-years gained without the cost of added life-years, and from €74 000 to €206 000 with costs of added life-years included. *Conclusion.* The combination strategy with a 5-year screening interval is potentially cost-effective compared with no screening, and with current screening practice when using a threshold value of €80 000 per life-years gained.

Abbreviations: CIN, cervical intraepithelial neoplasia; CIN1, cervical intraepithelial neoplasia grade 1; CIN2+, cervical intraepithelial neoplasia grade 2 or more advanced lesion; HPV, human papillomavirus; HR-HPV, high-risk human papillomavirus; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year; SEK, Swedish kronor.

Key Message

Repeat high-risk human papillomavirus testing using self-collection of vaginal samples at home for women aged $\geq$ 35 years is potentially cost-effective in the Swedish cervical cancer prevention program.

Introduction

The organized cytology-based cervical cancer screening program has been available in most Swedish counties

since the early 1960s and has proven effective in reducing the prevalence of cervical cancer by approximately 50% (1). However, since the end of 1990s this reduction has become somewhat stagnated, according to National Board of Health and Welfare (*Socialstyrelsen*). The participation rate of cervical cancer screening in Sweden, which is lower than that recommended by the European Union, may be a contributing factor (2) but it has also been reported that the organized Swedish cervical cancer screening program lacks sensitivity and precision in detecting cervical intraepithelial neoplasia (CIN) and cervical cancer (3).

Although human papillomavirus (HPV) testing has better sensitivity than conventional cytology, it has been reported to be less specific, especially among women under 30 years of age (4,5), which is problematic as a high number of false-positive results can lead to overtreatment and high costs. For this reason more effective screening methodologies, such as high-risk (HR)-HPV testing using self-collected vaginal samples, which can be collected by women in the privacy of their homes, have been evaluated (6). HR-HPV testing by a real-time PCR method using self-collected vaginal samples has been reported to detect more CIN2 or worse (CIN2+) compared with conventional cytology (7), and repeat HR-HPV testing within three to six months increases the specificity of cervical cancer screening even more (6). Although HR-HPV testing is used in triage situations in Sweden, it is not currently used in primary cervical cancer screening. The current guidelines of the organized Swedish cervical cancer screening program are based primarily on conventional cytology from Pap smears obtained in a clinical setting. The guidelines recommend that all women aged 23–60 years to be screened at 3-year (ages 23–50 years) or 5-year (ages 51–60 years) intervals (hereafter referred to as three/five-year intervals) and cytological results are categorized according to a Bethesda nomenclature (8). According to recent reports, about 3–5% of all Pap smears show some kind of abnormality, almost 80% of which are minor cytological changes (9).

Decision-makers in Sweden will have to consider previously published results of the high performance of repeat HR-HPV testing in screening compared with conventional cytology when deciding whether to incorporate HR-HPV testing in primary screening, and if the decision is positive, which strategy will be cost-effective. Therefore, the aim of this study was, from a societal perspective, to evaluate the cost-effectiveness of HR-HPV testing using self-collected vaginal samples in the organized Swedish cervical cancer screening program.

Material and methods

Model

We constructed a Markov model (using TREE AGE HEALTHCARE module software, 2011, see http://www.treeage.com/products/overviewHealth.html) with the health statuses well, HPV infection, CIN1, CIN2+ and FIGO stage I–IV, to simulate the natural history of cervical cancer. The age-specific incidence of HPV infection, health status transition probabilities, and survival rates for cervical cancer were derived from previously published literature to simulate the natural history of cervical cancer (6,10–22). For the base-case analysis, our model follows a simulated female cohort, all of whom started off with a health status of well at age 15 years. Health status then changed according to a set of probabilities that occurred at yearly cycles until age 85 years. The simulated cohort was at yearly risk of being infected with HPV, which could progress to CIN1 or CIN2+, persist or clear. Women with CIN1 or CIN2+ could either regress to a health status of well, persist or progress to a more severe health status. Women with HPV infection, CIN1 and CIN2+ could only have their condition detected during screening. Women with cancer could progress from FIGO stage I to a more severe FIGO stage (II–IV), or die from the disease based on 5-year survival probabilities. Women with FIGO stage I–IV could have their disease detected during screening or through symptoms. Due to necessary simplifications in the model, survivors of cervical cancer could only die from causes other than cervical cancer. In each yearly cycle of the model, women were at risk of dying from other causes. Mortality from other causes was estimated by subtracting the age-specific cervical cancer mortality risk from Swedish life expectancy tables (available at http://www.scb.se).

To adjust our model to Swedish conditions, we used data from the International Agency for Research on Cancer on the age-specific incidence and mortality rates for cervical cancer in Sweden before the initiation and widespread use of the population-based organized cervical cancer screening program (23–26). By adjusting the age-specific incidence rate of HPV infection within a relevant range reported in published studies, we calibrated the model closely to the average annual cervical cancer incidence rates by 5-year age groups before screening was initiated in Sweden, using empirical data from the years 1958–1960, thereby creating an unscreened reference strategy. We then applied cytology-based screening as per the current guidelines, coverage and screening-test performance as base case values (Table 1, Figure 1). Model validity was then tested by com-

Table 1. Model parameters.

Model parameter	Base-case analysis
Natural history (6,10–22)	
Well to HPV*	0.01–0.22
HPV to Well by age (year); 15–29/30–65/≥66	0.9/1 year/0.4/1 year/0.2/1 year
HPV to CIN1	0.2/3 year
HPV to CIN2+	0.05
CIN1 to Well	0.9
CIN1 to CIN2+ by age (year); 15–34/≥35	0.1/6 years/0.35/6 years
CIN2+ to CIN1	0.35/6 years
CIN2+ to Well	0.5
CIN2+ to FIGO I	0.4/10 years
FIGO I to FIGO II/annual probability of symptoms/5-year SR	0.9/4 years/0.15/0.84
FIGO II to FIGO III/annual probability of symptoms/5-year SR	0.9/3 years/0.225/0.66
FIGO III to FIGO IV/annual probability of symptoms/5-year SR	0.9/2 years/0.6/0.38
FIGO IV annual probability of symptoms/5-year SR	0.9/0.11
HR HPV strategy; Sensitivity for CIN1+/Specificity for CIN1+[a](6)	1.0/0.98
Conventional cytology; Sensitivity for CIN1+/Specificity for CIN1+[a](21,22)	0.75/0.72
Coverage (3)	0.80
Follow-up of HPV-positive or any abnormality	1.0
Follow-up of treatment of CIN or invasive cancer	1.0

*In the model, we do not distinguish between different HPV types. Incidence, progression and regression represent an average value for all HPV types. The age-specific incidence rate of HPV infection varied within a plausible range reported in the referenced studies, and was used to calibrate the model closely to the empiric cancer incidence and mortality rates in the Swedish population in the period before screening was initiated. Please see "Material and methods" for details.

[a]In the model, sensitivity is the probability of a positive test given the presence of CIN1+. Specificity is the probability of a negative test given the absence of CIN1+ based on the observed false-positive rate.

CIN, cervical intraepithelial neoplasia; CIN1+, cervical intraepithelial neoplasia 1 or worse; CIN2+, cervical intraepithelial neoplasia 2 or worse; HPV, human papillomavirus, SR, survival rate.

paring the projected results from screening with empirical data on average annual cervical cancer incidence rates by age group in the years after the initiation of organized cervical cancer screening in Sweden (year 1961–2009). In this comparison, our model projections were close to the empirical data, with a similar peak age group and overall lifetime risk.

Screening strategies

For the base-case analysis we evaluated two main screening strategies with different screening intervals: (i) cytology screening throughout the woman's lifetime in a clinical setting by a midwife ("conventional cytology strategy") and (ii) conventional cytology screening until age 35 years, followed by HR-HPV testing using self-collected vaginal samples in women ≥35 years of age ("combination strategy"). The age restriction for HPV self-sampling was applied according to Swedish recommendations that HPV testing be performed only in women ≥35 years of age (guidelines available in Swedish at http://www.sfog.se), and due to the high proportion of young women who test positive for HPV, but have normal cytology, leading to unnecessary colposcopy referrals (27). For both screening strategies, we considered screening intervals of two, three, five, and three/five years, as per the current recommended screening interval in Sweden. We considered the current screening practice Sweden, i.e. conventional cytology screening throughout a woman's lifetime at three/five-year intervals the "status quo strategy."

The combination strategy considered the use of self-collected vaginal samples, performed in the privacy of their own homes, in the framework of the organized cervical screening program. For self-collection a Viba-brush (Rovers Medical Devices, B.V., Oss, the Netherlands) is used to collect vaginal cells, which are applied to an indicating FTA™ Elute Micro Card (GE Healthcare, Chalfont St Giles, UK), and thereafter sent by post for HPV analyzing with an RT-PCR, which detects HR-HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59, as previously reported in detail (6,28,29).

Follow-up and treatment of CIN and cervical cancer

All follow-up was assumed to be 100% and to be performed within the same yearly cycle as the initial test. For the conventional cytology strategy, women with any cytological abnormalities were immediately referred for repeat cytology and colposcopy with biopsy. HR-HPV-positive women were considered to have repeated the HR-HPV test, and those positive at repeat HR-HPV testing were immediately referred for colposcopy with biopsy.

HR-HPV-positive women with negative cytology at follow-up were considered to be referred for further follow-up with a repeat HPV test after 12 months. Treatment of histologically confirmed CIN2+ or persistent CIN1 were assumed to be performed according to current Swedish practice. Women aged ≥40 years with confirmed CIN1 were assumed to be referred for immediate treatment, whereas women aged <40 years were assumed to be referred for follow-up with repeat cytology and colposcopy with biopsy after 12 months, before treatment of persistent CIN1 (30). After treatment, follow-up was

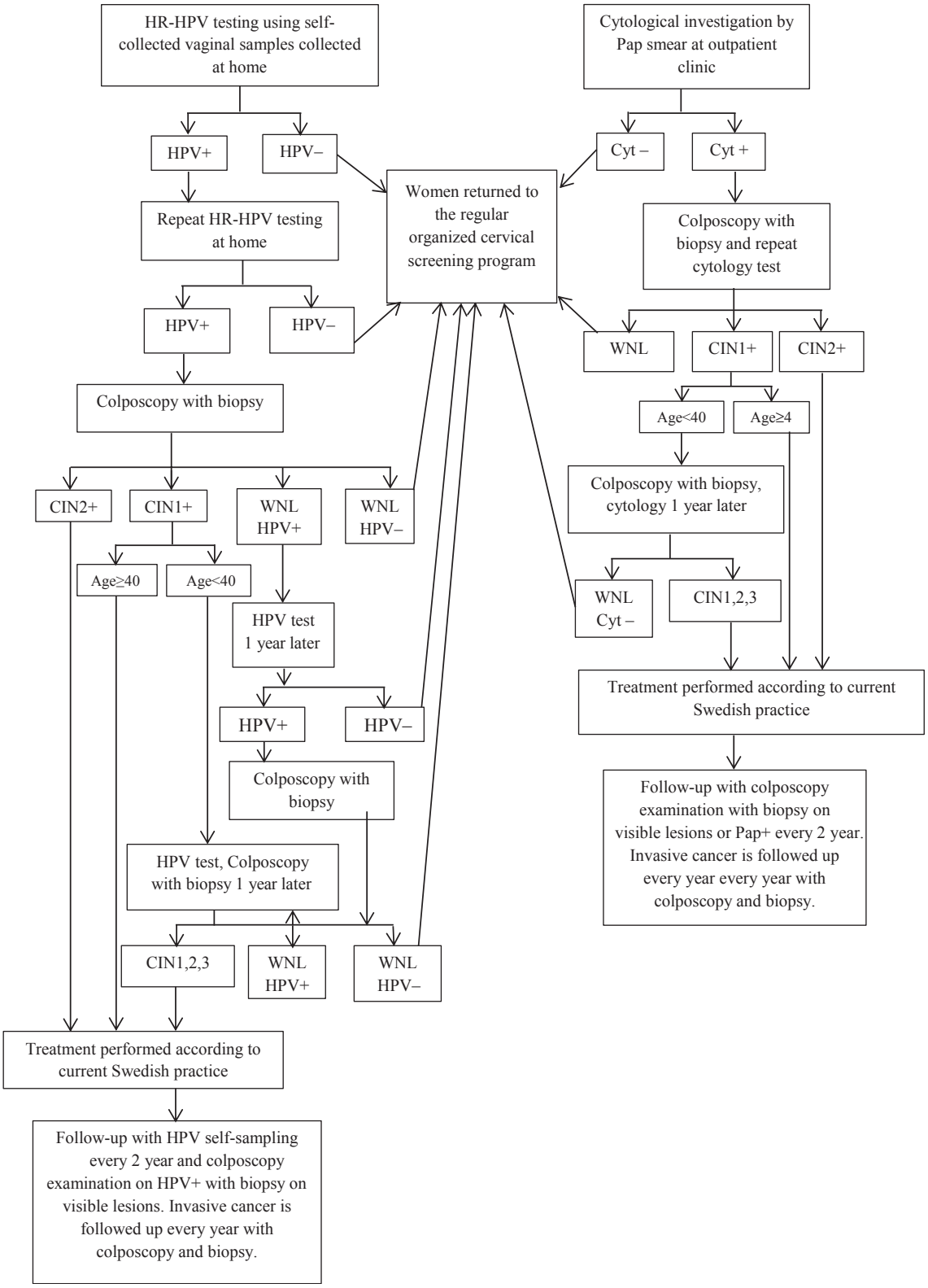

Figure 1. Screening according to the model structure.

assumed to be performed at 2-year intervals by both screening and gynecological examination throughout the woman's lifetime, regardless of the screening interval. Women in the model diagnosed with histologically confirmed cervical cancer during follow-up were considered to be referred for clinical staging according to FIGO procedures, as previously reported in detail (31). Stage-specific treatment was assumed to be performed according to current practice at the Department of Gynecological Oncology at Radiumhemmet, Karolinska University and Hospital, Stockholm, Sweden, previously reported in detail (32). Cancer survivors were followed up annually in the model by gynecological examination.

Cost data

Recent Swedish cost data were used to estimate the costs of the two different screening strategies, as well as follow-up and treatment of CIN and cervical cancer by FIGO stage (Table 2). Costs of the different screening strategies were mainly taken from our previously published article (33) and were complemented with the costs for the HPV sampling kit and typing at Uppsala University Hospital from the year 2011. Costs for diagnosis, staging and treatment of invasive cervical cancer were taken from Radiumhemmet, Karolinska University Hospital for the year 2011. Direct medical costs were mainly based on patient-level clinical costing, referred to in Sweden as cost per patient, a method for calculating the cost of a stay or visit at a care site for an individual or group of patients. The method describes healthcare utilization from a diagnostic perspective and is useful for decision-making in the healthcare sector. Indirect costs included costs related to the time a patient spends traveling to and from screening, wait time, and treatment time for CIN and cervical cancer. We employed wage rate estimates as a proxy for the value of patient time. The productivity lost due to cervical cancer screening, diagnosis, treatment and traveling to and from the site of care was based on an average monthly gross wage rate for women aged 18–65 years within all working groups, be it in the public (employed by the state) or private sector, and was adjusted for the number of employed women in the available female labor force in 2009, inflated to 2011 Swedish kronor (SEK) by the consumer price index. The gross wage rate was defined as income from employment, self-employment, pension, sick pay and other taxable incomes, and was retrieved from Statistics Sweden (available in English at http://www.scb.se). According to recommendations for cost-effectiveness analyses, we included the cost of added life-years (i.e. consumption net of production) (34) according to methodological recommendations from a previously published study (35). All costs were expressed as 2011 prices, and were converted from SEK to Euro (€) using the average exchange rate for 2011 (€1 = SEK9). For further information about direct medical and indirect costs, see Appendix S1.

Table 2. Costs for screening, staging and treatment of CIN and cervical cancer by FIGO stage.

Parameter	Direct cost (€)[a]	Indirect cost (€)[a,b]	Total cost (€)
Screening strategies			
High-risk-HPV test[c]	33		33
Office visit to midwife for a Pap smear[d]	79	56	135
Office visit for gynecological examination[d]	204	56	259
Office visit to gynecologist for colposcopy with biopsy[d]	279	60	339
Treatment for CIN			
Conization with laser (LEEP)[e]	2696	193	2890
Total cost for staging, treatment and follow-up by FIGO stage[f]			
FIGO I	24 571	8 023	32 595
FIGO II	47 044	12 578	59 622
FIGO III	42 339	12 578	54 917
FIGO IV	42 339	25 068	67 407

[a]All costs were, if necessary, were inflated to 2011 Swedish kronor (SEK) values by the consumer price index (available in English at http://www.scb.se).

[b]All costs were converted 2011 Euro (€) values. Indirect cost includes costs for patient time spent traveling, waiting, screening, staging and treatment. No indirect cost was defined for the HPV test since it was assumed to be performed at home during leisure time.

[c]Cost for the HPV sampling kit and typing is from the year 2011 performed at Uppsala University Hospital. Test includes physician assessment for abnormal results and test costs.

[d]Costs were taken from our previously published article (33). Clinical cytological fee includes physician assessment for abnormal results and test costs.

[e]Cost for conization with laser is patient-level clinical costing [known as cost per patient (KPP) in Sweden], from the Swedish KPP database during the year 2009. Cost includes follow-up at gynecological visit with colposcopy and biopsy two times in the same year of treatment.

[f]Cost for staging, treatment and follow-up per FIGO stage is mainly taken from Radiumhemmet, Karolinska University Hospital, Stockholm, Sweden, during 2011, complemented with KPP on radical hysterectomy from the year 2007, and cystoscopy from the year 2006.

CIN, cervical intraepithelial neoplasia; LEEP, loop electrode excision procedure; €, Euro.

Cost-effectiveness analysis

We adopted a societal perspective for the cost-effectiveness analysis according to health economic guidelines (36). All costs and health effects were discounted by 3%.

Due to uncertainties regarding quality of life weights associated with health statuses in the model, the base-case analysis estimated the average lifetime cost and total discounted and undiscounted health effects such as life expectancy between age 15 and age 85 years, with life-years gained (LYG) and reduction in risk of cervical cancer as primary outcomes. Performance of the alternative screening strategies was evaluated by the incremental cost-effectiveness ratio (ICER) [ICER = (cost of screening strategy A − cost of screening strategy B)/(effect of screening strategy A − effect of screening strategy B)]. The ICER for a given screening strategy was calculated relative to the next most effective strategy after eliminating strongly dominated strategies (i.e. strategies that were more costly and less effective than others) and weakly dominated strategies, which were ruled out by extended dominance (i.e. strategies whose costs and benefits were improved by a mixed strategy of two other alternatives) (37). The willingness-to-pay threshold value of one LYG and one quality-adjusted life-year (QALY) was set to €80 000 and €90 000, respectively, derived from the value used by the Swedish Road Authority for a statistical life in the valuation of health benefits for the assessment of transport safety programs, which is also in line with value-of-life literature (38,39).

Sensitivity analysis

In order to investigate the impact on cost-effectiveness, model parameters and costs were varied ±50–100%; screening coverage, sensitivity and specificity rates were varied 0–1. Additional analyses included: (i) applying follow-up with colposcopy with biopsy on all HPV-positive and cytology-negative women after 12 months; (ii) allowing HPV self-sampling on women aged ≥30 years; (iii) extending the screening age until 65 years as recommended in Europe (3); (iv) replacing conventional cytology with liquid-based cytology (€10 additional) but applying the same sensitivity as conventional cytology, as no significant differences in screening performance were observed between liquid-based cytology in combination with HPV testing and conventional cytology in our previous study (40); (v) inclusion of quality of life weights for each FIGO stage during the time in the corresponding stage to estimate QALYs: FIGO I 0.65, FIGO II–III 0.56, FIGO IV 0.48 (41).

Results

Projected model outcome

Projected reduction of cervical cancer risk for the conventional cytology strategy (status quo) was 48.1 and 75.4% for the combination strategy at three/five-year intervals, which is similar to other model projections that compared cytology with HPV testing strategies in European countries with similar screening policies (42,43).

Projections of intermediate outcomes such as age-specific HPV prevalence among women with normal cytology showed a peak prevalence of 28.6% at age 19 years. Age-specific peak prevalence of CIN was 3.7% at age 34, with a second peak at age 43 (3.2%). HPV prevalence in older women was similar to reported prevalence with HR-HPV in primary screening in a Swedish study (6). The model predicted an average prevalence of CIN that was similar to the prevalence observed in a Swedish population (44), and the rate of CIN detected by screening in the model was similar to reported rates in the screened population in Sweden (9).

According to model projections, referral rates for colposcopy and biopsy without presence of CIN or cervical cancer were around 35% higher for the combination strategy at the three/five-year interval compared with the 5-year interval. This result is comparable to another model projection showing a similar result (45).

Base-case results

In Table 3 and Figure 2, discounted and undiscounted cost-effectiveness results, with and without the inclusion of the cost of added life-years, are shown.

The different combination strategies dominated (weakly or strongly) the conventional cytology strategies. Depending on screening interval, the ICER for the combination strategies ranged from €43 000 to €180 000 per LYG without the cost of added life-years, and between €74 000 and €206 000 with the costs of added life-years included.

The cost-effectiveness ratios for the combination strategy at 5-year intervals, both with and without the cost of added life-years, were below the threshold value (€80 000), indicating that the combination strategy at 5-year intervals is cost-effective compared with no screening.

Sensitivity analyses

Results were most sensitive to variation in screening test performance, costs for screening, and least sensitive to variation in treatment costs for cervical cancer and changes of natural history parameters. However, the combination strategy at 5-year intervals remained cost-effective under most variations and additional analyses, whereas the conventional strategies were either strongly or weakly dominated, regardless of screening interval.

If specificity was increased to the optimal level of 98% for conventional cytology (46), the status quo strategy

Table 3. Average lifetime cost, discounted and undiscounted life-years gained (LYG), reduction in cervical cancer risk, incremental cost effectiveness ratio (ICER) of different screening strategies.

Screening strategy[a]	Average lifetime cost (€)[b]	Life expectancy, LYG, discounted 3%[b]	Life expectancy, LYG, discounted 0%[b]	Reduction in cervical cancer risk,%	ICER, €/LYG[c]	ICER with cost of added life-years, €/LYG[c,d]
No screening	303	28.7135	65.6275	—	—	—
Combination strategy, 5-year interval	1151	28.7331	65.7108	56.0	43 000	74 000
Status quo strategy, 3/5-year interval	1294	28.7340	65.7128	48.1	Dominated[f]	Dominated[f]
Conventional cytology strategy, 3-year interval	1334	28.7344	65.7111	50.3	Dominated[f]	Dominated[f]
Combination strategy, 3/5-year interval	1561	28.7380	65.7259	75.4	84 000	112 000
Combination strategy, 3-year interval	1589	28.7381	65.7299	76.8	Dominated[f]	Dominated[f]
Conventional cytology strategy, 2-year interval	1743	28.7377	65.7306	65.1	Dominated[e]	Dominated[e]
Combination strategy, 2-year interval	1918	28.7400	65.7374	85.1	180 000	206 000

[a]No screening refers to an unscreened population. Combination strategy refers to conventional cytology screening until age 35 years, followed by HR-HPV testing using self-collected vaginal samples in women $\geq$35 years of age. Conventional cytology strategy screening refers to cytology screening throughout the woman's lifetime. Status quo strategy refers to the current screening practice in Sweden, i.e. conventional cytology screening throughout a woman's lifetime at 3-year intervals (for ages 23–50 years) and 5-year intervals (for ages 51–60 years) or 3/5-year intervals.

[b]Total discounted and undiscounted health effects are presented as life expectancy between age 15 and age 85 years, defined as LYG.

[c]The ICER for a given screening strategy was calculated relative to the next most effective strategy after eliminating dominated strategies expressed as € per LYG.

[d]ICER with the inclusion of cost of added life-years (34,35). Strategies that are "dominated" are more costly and less effective than another strategy (37).

[e]Strongly dominated strategy (i.e. strategy that was more costly and less effective than others).

[f]Weakly dominated strategy (i.e. strategy whose costs and benefits were improved by a mixed strategy of two other alternatives).

€, Euro.

had a cost-effectiveness ratio of €64 000 and €34 000, with and without the cost of added life-years. The combination strategy at 3-year intervals and three/five-year intervals became weakly dominated, and at 5-year intervals strongly dominated. The combination strategy at 2-year intervals was the most effective, but with cost-effectiveness ratios higher than threshold value, both with and without the cost of added life-years.

When applying follow-up with colposcopy with biopsy on all HPV-positive and cytology-negative women after 12 months, the rank ordering did not change and the cost-effectiveness ratios increased minimally.

Allowing HPV self-sampling on women aged 30 years and older resulted in an increase in life expectancy for the combination strategy at 5-year intervals, being 0.0017 higher than the status quo strategy in the base-case analysis, with a cost-effectiveness ratio lower than the threshold value, at €76 000 and €45 000 per LYG with and without the cost of added life-years, respectively. The combination strategy at 2-year intervals was the most costly option with the highest life expectancy (28.7408).

When extending the screening age to 65 years as recommended in Europe (3), life expectancy increased by 0.001 compared with the base-case analysis for the combination strategy at 5-year intervals, with a cost-effectiveness ratio with and without the cost of added life-years of €75 000 and €43 000 per LYG respectively, i.e. lower than the threshold value.

As costs of colposcopy and biopsy differ between countries in Europe, depending on practiced follow-up management and treatment for CIN, we varied these costs $\pm$50–100% of their base case values. Overall, the rank ordering of strategies did not change. However, when reducing the cost by 50%, the combination strategy at three/five-year intervals had a cost-effectiveness ratio with and without the cost of added life-years of €65 000 and €37 000 per LYG, respectively, i.e. lower than the threshold value.

Applying the 85% coverage rate recommended in Europe (2) resulted in a higher life expectancy for the combination strategy at 5-year intervals, but still had a cost-effectiveness ratio lower than the threshold value, both with and without the cost of added life-years.

Applying quality of life weights to duration of corresponding health statuses, depending on the screening interval, the ICER for the combination strategies ranged from €26 000 to €110 000 per QALY without costs of added life-years, and between €44 000 and €125 000 with the costs of added life-years included. The cost-effectiveness ratios for the combination strategy at three/five-year intervals and at 5-year intervals were both below the threshold value of a QALY (€90 000), with and without

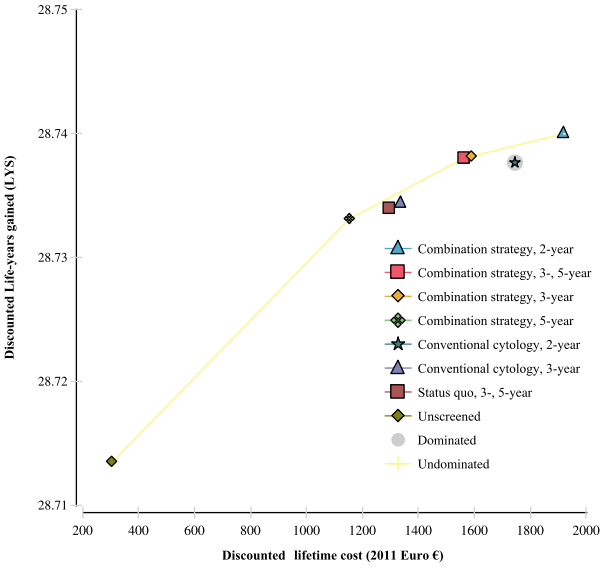

Figure 2. Cost-effectiveness of different screening strategies at different screening intervals: base-case analysis without the cost of added life-years.

Note: For the conventional cytology strategy: cytology screening throughout the woman's lifetime combination strategy: conventional cytology screening until age 35 years, followed by HR-HPV testing using self-collected vaginal samples in women $\geq$35 years of age. Status quo strategy: current screening practice Sweden, i.e., conventional cytology screening throughout a woman's lifetime at 3-year intervals (for ages 23–50 years) and 5-year intervals (for ages 51–60 years).

cost of added life-years, whereas the combination strategy at 2-year intervals was higher than the threshold value.

Discussion

Our study indicated that the combination strategy at three/five-year intervals and at 5-year intervals were cost-effective, with cost-effectiveness ratios below the willingness-to-pay threshold values similar to previous studies (27,42,43). Referral rates were lower with a 5-year screening interval than with a three/five-year interval, indicating that unnecessary follow-up and treatment could be reduced by extending screening intervals, which could result in cost savings for equal, or more effective outcomes, in agreement with other studies (5,45,47).

To our knowledge, there have been no published cost-effectiveness studies of HR-HPV testing using self-collected vaginal samples in Sweden. In comparison, a study from the United States evaluating the cost-effectiveness of testing vaginal samples collected by women in their homes found that triennial screening followed by cytology triage in a clinical setting was cost-effective compared with cytology-based screening (48). This result was similar to those of our study. When comparing our results with primary HPV screening performed in a clinical setting, a recently published cost-effectiveness study put forth favorable arguments for HPV testing in Norway (49). Our own previous cost-effectiveness study found that for management of women aged $\geq$30 years with atypical squamous cells of undetermined significance, HPV triage was superior to cytology screening (33). Another Swedish study found that HPV testing in combination with cytology three times in a lifetime was the most favorable alternative (50).

Self-collection of vaginal samples on an FTA™ card, thereafter sent for HPV analysis by RT-PCR (6,28,29), eliminates the need for an office visit, and genotyping can be done at the same time, making the practice less aggressive than immediate colposcopy with biopsy on all women with abnormal test results, which is associated with high costs, as well as negative psychological and physical effects. Moreover, self-collection of vaginal samples could reduce unnecessary colposcopic examination (51). The ATHENA study showed that the overall prevalence of HR-HPV (14 genotypes) detected by the COBAS® HR-HPV test (Roche Molecular Systems, Pleasanton, CA, USA) among women aged $\geq$30 years with normal cytology was 6.7% and the absolute risk of CIN2+ was 6.1%, which increased in HPV16-positive women to 13.6%. This finding provides additional support for the use of HPV genotyping assays in screening (52).

Even with good screening tools, some women will refuse to participate in screening, or will not be covered by the screening program in Sweden, which has been suggested as the major reasons for cervical cancer morbidity (3). For a home-based screening test to be successful, the acceptability among the population must be high. As of yet, no Swedish studies have addressed this issue. However, the previously mentioned study showed that 61% of women preferred a home-based test due to greater ease and less inconvenience, as long as it has the same effectiveness as a clinic-based test (48).

Coverage of cervical cancer screening programs in the European Union member states is below 80%, compared with the recommended 85% (2). The present study showed that a higher participation in screening increases life expectancy. Women who avoid participation often have lower socioeconomic status, or have higher socioeconomic status, but do not consider themselves to be at risk (53). Lack of knowledge and information about the benefits and role of screening are important factors in non-compliance (54,55).

Although modeling is a simplification, our model reflects, to the best of our knowledge, current Swedish clinical practice within the cervical cancer prevention program, including follow-up methods for CIN and treatment of cervical cancer. Accurate deliberation of all incremental effects

and costs regarding new screening strategies compared with status quo policy is necessary. In Sweden, no long-term empirical data on safety and outcomes of HPV testing in the organized screening program exists. With this cost-effectiveness study, we aim to provide information about the relative costs and effects of HR-HPV testing using self-collected vaginal samples, so that decision makers can explore the possible implications of incorporating HPV testing into the organized screening program.

There were limitations to this study. Data were not available or were not included for all required model parameters, which could contribute to heterogeneity in a simulated population. There is a great uncertainty regarding the natural history of HPV infection and cervical cancer. In the model, we do not distinguish between different HPV types clearly related to the risk of developing cervical cancer. Also, we did not consider any individual characteristics that might influence disease progression. Swedish FIGO stage-specific survival estimates for cervical cancer were not available and could affect the overall life expectancy in this study. No Swedish data were available on quality of life reduction associated with precancerous lesions or cancer, or associated with women being informed that they are infected with HR-HPV types. Similarly, cost and quality of life reduction for relapse, treatment complications and individual alternative practice due to the complex nature of cervical cancer itself was not accounted for. As more international and country-specific data become available, results presented in this study may have to be refined.

In this study, we did not consider the future impact of HPV vaccination in the model design. After the implementation of HPV vaccination among young women in Sweden, HPV testing will become important in primary screening, both for the surveillance of cervical cancer and for the follow-up of vaccinated women (56). In this scenario, repeat HPV self-sampling with a high sensitivity and specificity that is easy to perform at home would be advantageous both as a screening strategy and as a tool to monitor HPV prevalence within the population.

In conclusion, our results indicate that HPV self-sampling at home is cost-effective among women age ≥ 35 compared with status quo policy.

Acknowledgments

We thank Ingrid Lekander at Karolinska Institute for assistance with the model.

Funding

This study was supported by the Swedish Cancer Foundation (070623, CAN 2007/1044, 11 0544, CAN 2011/471), KI Cancer Strategic Grants (5888/05-722), Swedish Research Council (521-2008-2899), Medical Research Council, and Cancer Society in Stockholm, Stockholm County Council.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplementary information about direct medical and indirect costs.