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Cost-effectiveness evaluation of HPV self-testing offered to non-attendees in cervical cancer screening in Switzerland

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HIGHLIGHTS

- We evaluate cost-effectiveness of offering Self-HPV to non-attendees in Switzerland.
- The incremental cost-effectiveness ratio was 11'138 US$/QALY for the Self-HPV followed by a pap test strategy.
- Offering a Self-HPV screening to non-attendees is effective in reducing cervical cancer incidence and mortality.
- Offering Self-HPV as a cervical cancer screening strategy to non-attendees in Switzerland is a cost-effective intervention.

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ABSTRACT

Objective. About 30% of women who are eligible for cervical cancer (CC) screening remain un-screened or under-screened in Switzerland. HPV testing on self-collected vaginal samples (Self-HPV) has shown to be more sensitive than cytology while also reaching non-attendees. The objective of this study was to explore the cost-effectiveness of offering Self-HPV to non-attendees in Switzerland.

Methods. A recursive decision-tree with one-year cycles was used to model the life-long natural HPV history. Markov cohort simulations were used to assess the expected outcomes from the model. The outcomes of three strategies were compared with the absence of screening: Self-HPV and triage with colposcopy (Self-HPV/colpo), Self-HPV and triage with Pap cytology (Self-HPV/PAP), cytological screening and triage with HPV (PAP/HPV). Sensitivity analyses for the key parameters of the model were conducted to check the robustness of findings.

Results. Offering a Self-HPV screening to non-attendees could prevent 90% of CC and 94% of CC-related deaths in the study population. The current cytology-based program could reduce by 83% the number of CC cases and by 88% the number of CC-related deaths over the population's lifetime. Compared to the absence of screening, incremental cost-effectiveness ratios (ICER) were estimated to be, per saved Quality Adjusted Life Year (QALY), 12413US$ for the strategy Self-HPV/colpo, 11138US$ for the strategy Self-HPV/Pap and 22488US$ for the strategy PAP/HPV.

Conclusions. Offering Self-HPV as a CC screening strategy to non-attendees in Switzerland is a cost-effective solution that is associated with a reduction of CC cases and related deaths. Self-HPV is more cost-effective than the currently used cytology-based screening.

1. Introduction

Cervical cancer (CC) screening was established 60 years ago in Western countries and is considered a major public health success. Indeed, since its introduction, the incidence of CC has declined by almost 60% [1]. Such impact is attributable to the Pap smear test [2], which has been adopted as standard practice for CC screening. The Swiss guidelines advise to perform the Pap smear test every 3 years on women aged 21–70 years, as part of an opportunistic screening system that is essentially based on the women's and their physicians' initiative [3].

Since the introduction of the HPV vaccination in 2007, CC screening guidelines have evolved and several countries, such as England,

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Scandinavia and the Netherlands, are now evaluating or already undergoing a transition from a cytology-based cervical screening to an HPV-based strategy. The Netherlands have been the pioneers in the implementation of an HPV-based CC screening system, with their guidelines advising to perform HPV testing every 5 years on women aged 30–60 years [4]. Such turnaround took place as a response to overwhelming evidence coming from several randomized control trials demonstrating that HPV-testing is more effective than cytology for CC screening [5–7]. HPV-based primary screening is highly sensitive, although it has a limited specificity and positive predictive value. For these reasons, a triage strategy involving cytology, genotyping and/or colposcopy, by identifying high-risk HPV-positive women at highest risk for cancer, would improve the performance of HPV testing alone [8]. Additionally, the choice of the HPV test is a crucial one. While there are at least 150 different HPV tests available worldwide [9], only a few are clinically validated. The choice of the HPV test to be used should be based on its cost-effectiveness and clinical validity [10].

Cervical screening is only efficient if a large part of the eligible population take part in it. Until recently, the cytology-based cervical screening was able to achieve a coverage rate of about 70% in Western countries [11,12] while about 30% of women eligible for CC screening remained un-screened or under-screened [11,12]. This coverage rate has remained almost unchanged since the year 1985 [13].

Many studies have focused on identifying factors that may impact CC screening participation in Switzerland [11,14,15]. In the DEPIST study conducted in Switzerland, the main reasons for nonparticipation in CC screening were practical ones, such as lack of time and the cost of screening [16,17]. Possible approaches used to improve the participation of non-attendees would therefore include a screening method that is free of charge and that avoids a gynecological consultation.

Despite the expected health benefit deriving from an improved coverage rate, offering screening would seemingly increase the economic burden weighting on the federal health care system. The cases of CC avoided with a higher coverage rate, however, would globally reduce the cost related to CC, such as that of conizations, other surgical and medical cancer treatments, and palliative care. A health economics study is therefore needed in order to assess the cost-effectiveness of screening strategies that can be proposed to non-attendees.

Recent studies have shown that offering self-sampling for high risk HPV testing (Self-HPV) is a valid alternative to the pap smear, leading to a good coverage rate [18,19]. The advantage of Self-HPV is a lower cost and a higher sensitivity than Pap smear [20]. To boost its performance, Self-HPV can be paired with a triage with Pap cytology or colposcopy. We compared these two strategies with the no-screening one and the currently recommended, cytology-based one. A modeling study was conducted to assess the cost-effectiveness of the four screening strategies from a health care provider's perspective.

2. Methods

2.1. Target population

Unscreened women, aged 25 years and living in Switzerland, without CC.

2.2. Strategies modelled

The following four strategies were compared using a life-long decision-based analytical model:

1) *No screening*, but treatment of symptomatic CC;
2) *Screening strategy 1*: *Self-HPV and triage with Pap cytology* (Self-HPV/PAP). Self-HPV testing performed every 3 years starting at age 25. Liquid-based cytology (Pap test) to triage HPV-positive women, followed by colposcopy for women with atypical squamous cells of undetermined significance or worse cytology (ASC-US+); conization if a cervical intraepithelial neoplasia grade 2 or worse (CIN2+) is identified in biopsy; Self-HPV is performed after 12 months in case of cervical intraepithelial neoplasia grade1 (CIN 1), negative colposcopy or negative biopsy. HPV and Pap tests from the same sample (liquid medium) are used as tests of cure at 12 months after treatment. If the HPV and Pap tests are negative, screening is performed every 3 years. In contrast, if the HPV and/or Pap test turn out positive, a new colposcopy is scheduled.
3) *Screening strategy 2*: *Self-HPV and triage with colposcopy* (Self-HPV/colpo). This strategy skips the step of triage with Pap cytology in the view of minimizing the number of clinical visits and to meet the needs of women who risk the most to be lost to follow-up. In some cases, an immediate treatment can be offered. Self-HPV testing is scheduled every 3 years starting at age 25. Colposcopy is used to triage HPV-positive women; conization is performed if CIN2+ is identified on biopsy samples; Self-HPV is performed after 12 months in case of a CIN 1 lesion, a negative colposcopy or a negative biopsy. HPV and Pap tests from the same sample (liquid medium) are used as tests of cure after 12 months. If the HPV and Pap tests are negative, screening is resumed to every 3 years. In contrast, if the HPV and/or Pap test are positive, a new colposcopy is scheduled.
4) *Screening strategy 3* (*the currently used strategy*): *Pap* (*liquid-based*) *cytology and triage with HPV* (PAP/HPV). Pap cytology testing is scheduled every 3 years starting at age 25. Women with ASC-US undergo HPV testing for triage, which is performed on the same liquid medium-based sample. HPV positive women are be referred to colposcopy while HPV negative women return for a routine control after 3 years. Women with a high-grade squamous intraepithelial lesion (HSIL), ASC-H (atypical squamous cells- cannot exclude HSIL), or atypical glandular cells (AGC), are referred for colposcopy. A conization is proposed if a CIN2+ lesion is identified at biopsy. In case of a CIN 1 lesion, negative colposcopy or negative biopsy, a Pap test will be performed after 12 months.

HPV and Pap tests from the same, liquid medium-based samples are used as tests of cure at 12 months after treatment. If the HPV and Pap tests are negative, women resume to routine screening every 3 years. In contrast, if the HPV and/or Pap test are positive, a new colposcopy is scheduled.

The compliance with each screening procedure was assumed to be 70%. All screening tests were proposed until the age of 70 years. If a FIGO I to IV CC is detected, appropriate treatment is planned.

2.3. Outcomes

The effectiveness of each strategy was measured by the quality-adjusted life of years (QALY) on a life-long time horizon and the cost averaged by woman. The incremental cost-effectiveness ratio (ICER) was used to compare screening strategies. We adopted the healthcare payer's perspective. An annual discount rate of 3% was applied to both effectiveness and cost outcomes.

2.4. Model

A recursive decision-tree with one-year cycles was used to model the life-long natural HPV history. The transition probabilities used in the model were derived from Canfell et al. [21] and Myers et al. [22] or were adjusted to Swiss context (Supplementary Table 1 (ST1)).

Briefly, the health states captured the various stages of the HPV natural history (well, HPV infected, CIN1, CIN2, CIN3, FIGO I to IV, death). A CC (FIGO stages I to IV) can be detected from symptoms and the patient was then treated. Women staying 5 years with an undetected CC were considered cured and were no more at risk of CC. Annual mortality from another cause than CC was obtained according to the age from the Swiss Federal Statistical Office (data not shown). The model was calibrated for the percentage of women experiencing a HPV infection in

their life to be 90%. This model was used for the strategy with no screening. For the other strategies, screening procedures were introduced in this model.

The positivity rates of the tests according to the health states were obtained from published international [23] or Swiss [24] studies. When a positivity rate in a specific health state was reported in various papers, methods of meta-analysis were used to combine studies. To account for the uncertainty around the estimates of the positivity rate, the distribution of the estimates was derived from the 95% confidence intervals reported in the published papers or from the 95% confidence intervals around the pooled estimates when meta-analysis methods have been used. Positivity rates and transition probabilities are shown in Table 1.

2.5. Utility parameters

Utility parameters were introduced in the model to account for the loss of quality of life related to CC. The utility for women with a detected cancer was 0.7598 in FIGO I stage and 0.6693 in FIGO II to IV stages. When a woman was detected with CIN1 (respectively CIN2+), a utility of 0.9333 (respectively 0.8658) was applied over two months. A positive result to a HPV test yields to a utility of 0.9764 over two months. A positive result to a PAP test yields to a utility of 0.9233 over two months (average of 0.9404 with ASC-US diagnosis and 0.9062 with LSIL/HSIL diagnosis). All values of utilities were obtained from the Swiss study of Szucs et al. [25].

2.6. Cost parameters

Health costs in Switzerland are regulated by the Federal Council through a tariff system applied in every Swiss canton, which was first introduced in 2004. Cost parameters introduced in the model corresponded to the cost of screening procedures, colposcopy, conization treatment of CC and palliative care. Details are given in ST2. Briefly, the cost was 53 US$ per Self HPV test, 153.84 US$ (236.89 US$) per negative (positive) PAP test, 289.89 US$ per screening procedure consecutive to a conization, 328.8 US$ per colposcopy, 2721.6 US$ per conization. The year following the detection of a CC, the cost of the treatment was 30,000 US$ if the FIGO stage was I and 55,500 US$ for the other FIGO stages. The cost of palliative care was 37,750 US$. All costs were provided by the accounting division of the University Hospitals of Geneva and converted in US$ with an exchange rate of US$1 = 1 Swiss franc (July 20, 2018).

2.7. Analytical methods

Markov cohort simulations were used to assess the expected outcomes from the model. Briefly, at each cycle, the cohort was distributed in the health states for the next cycles according to the health of the current cycle and proportionally to the transition probabilities of the current cycle. A probabilistic sensitivity analysis was conducted to account for the uncertainty on the estimated positivity rates of Self-HPV and PAP tests. Five thousand sets of positivity rates were randomly generated according to the distributions shown in Table 1. These distributions by health state were derived from estimated positivity rates reported in Zhao et al. [23] and Bigras et al. [24]: the logit of positivity rates were assumed normally distributed. The standard deviations of these gaussian distributions were the standard error of the estimated logit of the positivity rates. For each of the five thousands sets of positivity rates, the model was assessed using Markov cohort simulations and the expected outcomes were assessed. The 0.025 and 0.975 quantiles were assessed to provide a 95% confidence interval around the expected outcomes. In addition, a one-way sensitive analysis was conducted to check the robustness of the findings in regards of the assumptions on the values of the key parameters. The coverage rate of the screening procedures ranged from 50% to 90%, the annual discount rate from 0% to 5%, the cost of Self HPV test from 30 to 73 US$. The model was also calibrated for the percentage of women with a HPV infection in their life to be 80% and 98%. Finally, the frequency of screening tests ranged from 3 to 10 years.

3. Results

3.1. Base case analysis

In the base case scenario, the screening tests were planned every 3 years in 25 years old women. With screening strategies Self-HPV/colpo, Self-HPV/PAP, the number of women with a CC in their life was divided by approximately ten when compared with the absence of screening. The mortality related to CC was also decreased with the first two strategies (Table 2).

The overall average number of screening tests that a woman goes through in her lifetime was similar with the different screening strategies studied, although the number of colposcopies was lower in the Self-HPV/PAP and PAP/HPV strategies.

The life expectancy was slightly higher when screening strategies Self-HPV/colpo, Self-HPV/PAP and PAP/HPV were applied (Table 3). When expressed in number of days, the improvement in life expectancy compared with the absence of screening obtained was:

strategy Self−HPV/colpo 82 days
strategy Self−HPV/PAP 81 days
strategy PAP/HPV 75 days

In the absence of screening, the main part of the total cost was related to the treatment of CC. With other strategies, the cost related to CC treatment was lower, but the total cost was higher due to a higher cost of the screening tests (especially for the strategy PAP/HPV),

Table 1
Positivity rates of HPV and PAP tests introduced in the decision-analytical model.

	Positivity rate	Probabilistic distribution of the logit of positivity rate	Reference
HPV test*			
Well or HPV infected	0.108	N(−2.11,0.26)	Zhao et al
CIN1	0.801	N(1.39,0.47)	Zhao et al
CIN2 or more advanced stage	0.923	N(2.48,0.82)	Zhao et al
PAP test**			
Well or HPV infected	0.063	N(−2.70,0.94)	Zhao et al., Bigras et al
CIN1	0.396	N(−0.42;0.09)	Zhao et al., Bigras et al
CIN2 or more advanced stage	0.695	N(0.82,0.57)	Zhao et al., Bigras et al

* The positivity rates of HPV test were reported in Zhao et al. [23]. In the probabilistic sensitivity analysis, the distribution of the logit of positivity rates was assumed Gaussian. The first number in brackets is the mean of the distribution (logit of the positivity rate) and the second number is the standard deviation of the distribution. The standard deviation of the distribution was the standard error of the estimated logit of the positivity rate assessed using the reported 95% confidence interval.

** The positivity rates of PAP test were reported in Zhao et al. [23] and Bigras et al. [24]. The logit of positivity rates were combined over the two studies using meta-analytic methods (method of the inverse of variance with fixed effect). With these methods, the pooled logit of positivity rates were assumed normally distributed. The standard deviation of the distribution was the standard error of the pooled logit of the positivity rate.

Table 2
Clinical outcomes for each screening strategy.

	Screening strategies			
	No screening	Self-HPV/colpo	Self-HPV/PAP	PAP/HPV
Cancer (per 1000 women)	20.39	1.85 (1.54–2.61)	2.06 (1.66 to 3.06)	3.48 (2.53 to 6.02)
Detected cancer (per 1000 women)	14.61	1.39 (1.14–2.00)	1.57 (1.25 to 2.36)	2.69 (1.95 to 4.60)
Cancer related mortality (per 1000 women)	9.73	0.55 (0.44–0.85)	0.63 (0.49 to 1.04)	1.19 (0.78 to 2.40)
Palliative care (per 1000 women)	3.48	0.13 (0.10–0.22)	0.15 (0.12 to 0.28)	0.33 (0.19 to 0.75)
Number of tests (per women)				
HPV test	0	12.82 (12.42–13.48)	12.85 (12.44 to 13.52)	0.45 (0.17 to 1.56)
HPV + PAP test	0	0.16 (0.14–0.17)	0.15 (0.14 to 0.16)	0.13 (0.10 to 0.14)
PAP test	0	0	1.44 (1.03 to 2.06)	11.24 (10.44 to 11.37)
Number of colposcopies (per women)	0	1.96 (1.42–2.84)	0.76 (0.54 to 1.2)	0.73 (0.36 to 3.15)
Number of conizations (per women)	0	0.16 (0.14–0.17)	0.15 (0.14 to 0.16)	0.13 (0.10 to 0.14)
Number of visits (per women)	0	2.29 (1.73–3.16)	2.51 (1.94 to 3.50)	12.22 (11.96 to 13.85)

Reported results are those of the base case analysis. 95% confidence interval obtained from the probabilistic sensitivity analysis are reported in brackets. Since only positivity rates are variable in the probabilistic sensitivity analysis, no confidence interval are obtained for the ≪no screening≫ strategy.

Table 3
Cost and effectiveness for each screening strategy.

	Screening strategies			
	No screening	Self-HPV/colpo	Self-HPV/PAP	PAP/HPV
Life expectancy (years)	58.74	58.96 (58.95 to 58.97)	58.96 (58.95 to 58.97)	58.94 (58.91 to 58.96)
Discounted life expectancy (years)	27.82	27.88 (27.88 to 27.88)	27.88 (27.88 to 27.88)	27.87 (27.86 to 27.88)
Quality adjusted life years (QALY)	58.72	58.95 (58.94 to 58.95)	58.95 (58.93 to 58.95)	58.93 (58.88 to 58.94)
Discounted QALY	27.81	27.87 (27.87 to 27.87)	27.87 (27.87 to 27.87)	27.87 (27.85 to 27.87)
Average total cost per woman (US$)	320	1071 (953 to 1248)	978 (885 to 1128)	1510 (1368 to 2336)
Cost of cancer treatment	271	29 (24 to 42)	33 (27 to 50)	56 (40 to 96)
Cost of palliative care	48.4	2.1 (1.7 to 3.7)	2.6 (1.9 to 4.8)	5.5 (3.2 to 12.2)
Cost of tests	0	400 (387 to 419)	537 (490 to 612)	1105 (1030 to 1500)
Cost of colposcopy	0	374 (275 to 530)	153 (109 to 233)	139 (72 to 566)
Cost of conization	0	265 (236 to 280)	252 (218 to 270)	205 (154 to 232)

Reported results are those of the base case analysis. 95% confidence interval obtained from the probabilistic sensitivity analysis are reported in brackets. Since only positivity rates are variable in the probabilistic sensitivity analysis, no confidence interval are obtained for the « no screening » strategy. All reported costs were discounted with an annual rate of 3%.

colposcopy and conization. Compared with the absence of screening, the average cost per woman was higher by:

strategy Self−HPV/colpo 751 US
strategy Self−HPV/PAP658 US strategy PAP/HPV 1191 US

Despite a higher cost of screening tests with the Self-HPV/PAP strategy than with the Self-HPV/colpo one, the average total cost was lower with the former one because of the lower frequency of colposcopy. The difference in cost between these two strategies was 92 US$ (Table 4).

The incremental cost and effectiveness of the screening strategies compared with the absence of screening are shown in Table 4 and represented in Fig. 1. The ICERs per saved QALY were:

strategy Self−HPV/colpo 12, 413US
strategy Self−HPV/PAP11, 138US strategy PAP/HPV 22, 488US

Table 4
Incremental cost and effectiveness and ICER for the comparison of screening strategies.

	Compared screening strategies					
	Self-HPV/colpo vs no screening	Self-HPV/PAP vs no screening	Self-HPV/colpo vs self-HPV/PAP	PAP/HPV vs no screening	PAP/HPV vs self-HPV/colpo	PAP/HPV vs self-HPV/PAP
Avoided cases of cancer (per 1000 women)	−18.54 (−18.85 to −17.77)	−18.33 (−18.72 to −17.33)	−0.21 (−0.54 to −0.08)	−16.91 (−17.86 to −14.37)	1.63 (0.47 to 4.08)	1.42 (0.30 to 3.66)
Life expectancy (days)	82.15 (78.71 to 83.34)	81.17 (76.5 to 82.77)	0.98 (0.36 to 2.65)	74.97 (62.33 to 79.64)	−7.18 (−19.46 to −1.68)	−6.2 (−17.52 to −0.88)
Discounted life expectancy (days)	22.86 (21.76 to 23.24)	22.53 (21.06 to 23.05)	0.33 (0.13 to 0.87)	20.60 (16.8 to 22.06)	−2.26 (−5.95 to −0.53)	−1.93 (−5.31 to −0.26)
QALY (days)	83.38 (80.12 to 84.56)	82.04 (77.21 to 83.61)	1.34 (0.52 to 3.54)	74.95 (59.6 to 80.74)	−8.43 (−23.51 to −2.13)	−7.1 (−20.75 to −0.95)
Discounted QALY (days)	22.10 (21.09 to 22.66)	21.59 (20.02 to 22.19)	0.50 (0.16 to 1.40)	19.34 (13.3 to 21.54)	−2.76 (−8.73 to −0.38)	−2.26 (−7.54 to −0.07)
Average total cost per woman (US$)	751 (634 to 928)	658 (566 to 808)	92 (29 to 1487)	1191 (1048 to 2017)	440 (208 to 1265)	532 (348 to 1296)
ICER (US$ per saved year of life)	11,999 (10,213 to 14,868)	10,675 (9315 to 13,149)	102,567 (25,470 to 275,122)	21,108 (18,170 to 37,162)	−71,078 (−386,309 to −18,998)	−100,717 (−584,611 to −27,874)
ICER (US$ per saved QALY)	12,413 (10,328 to 15,780)	11,138 (9504 to 14,257)	67,092 (9363 to 244,070)	22,488 (18,278 to 53,439)	−58,172 (−244,899 to −19,036)	−86,123 (−510,629 to −23,657)

Reported results are those of the base case analysis. 95% confidence interval obtained from the probabilistic sensitivity analysis are reported in brackets.

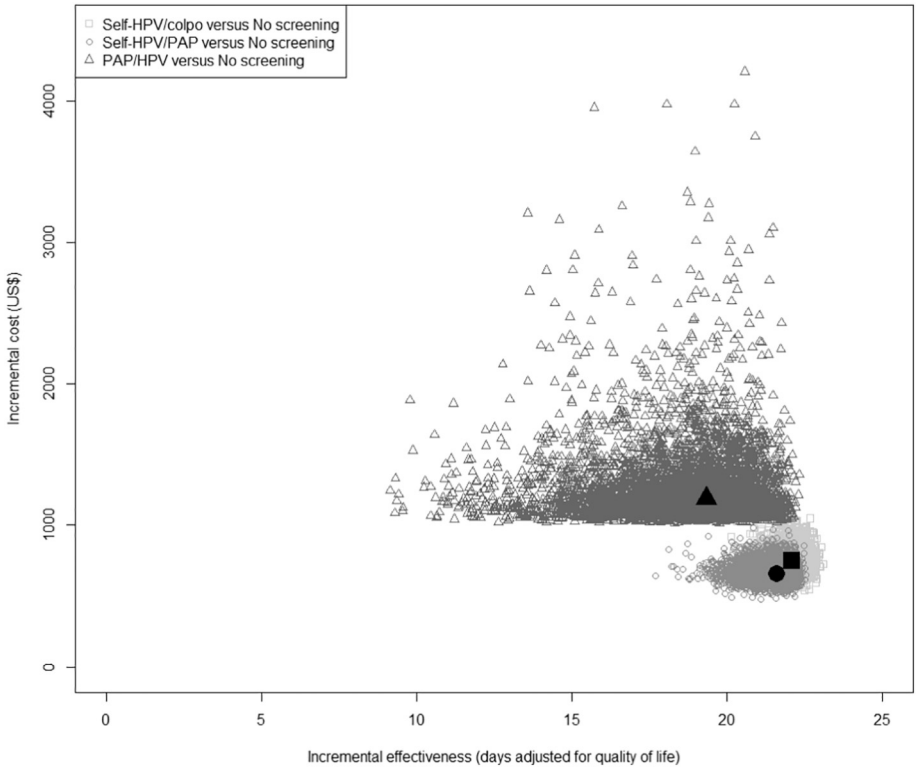

Fig. 1. Representation of the incremental cost and effectiveness for each screening strategy compared with the absence of screening. The black symbols represent the results for the base case scenario. The grey symbols represent the results of the probabilistic sensitivity analysis accounting for uncertainty on parameters of the decision analytic model.

Since the ICERs were lower than 50′000, the three screening strategies all seemed more cost-effective when compared with the lack of screening. The ICER for the strategy Self-HPV/colpo compared with the strategy Self-HPV/PAP was 67,092 US$ per QALY. Therefore, the strategy Self-HPV/colpo was not cost-effective compared with the strategy Self-HPV/PAP. This was explained by the low incremental effectiveness (1 day of life). Compared with the strategies self-HPV/colpo and self-HPV/PAP, the strategy PAP/HPV was not cost-effective because it was less effective and more costly. Findings were similar with the ICERs not adjusted for quality of life (Table 4 and Supplementary Fig. 1 (SF1).

Cost-effectiveness acceptability curves are shown in Fig. 2. For each strategy, the corresponding curve shows the estimated probability for this strategy to be the most cost-effective among the investigated strategies. This probability is represented according to the value of willingness-to-pay. For low values of willingness-to-pay, the strategy with no screening procedure was preferred because the incremental effectiveness was low. For values corresponding to accepted willingness-to-pay in developed countries (approximately between 30,000 and 50,000 US$ per saved QALY), the strategy Self-HPV/PAP was preferred. In Switzerland, the accepted value of willingness-to-pay is around 50,000 US$ per saved QALY. At this value, the probability for the strategy Self-HPV/PAP to be cost-effective was 0.59. The self-HPV/colpo strategy was preferred only for values of willingness-to-pay greater than commonly accepted thresholds. Cost-effectiveness acceptability curves when the incremental effectiveness was not adjusted for the quality of life are shown in SF2.

3.2. One-way sensitivity analysis

When the key parameters varied in the pre-specified range, the ICER adjusted for the quality of life ranged from (per saved QALY and when compared with absence of screening, SF3):

strategy Self−HPV/colpo 4537 to 23,014 US
strategy Self−HPV/PAP3874 to 21,074 US
strategy PAP/HPV 9193 to 40,727 US

The ICERs were especially sensitive to the annual discount rate. This can be explained by the age at which the cost was calculated and CC occurred. Since CCs occurred between 25 and 70 years of age, the related cost and the potential benefits of screening strategies are importantly discounted. However, even for a high annual discount rate, the screening strategies were all more cost-effective than the absence of screening. Detailed results of the one-way sensitivity analysis are shown in ST3.

3.3. Screening frequency

When the frequency of scheduled screening tests increased from 3 (base case scenario) to 10 years, the number of screening tests per woman was divided by more than 2:

strategy Self−HPV/colpo from 12.8 to 4.6
strategy Self−HPV/PAP from 12.8 to 4.7
strategy PAP/HPV from 11.2 to 4.0

The number of women with a CC (per 1000 women) in their life was 3 times higher:

strategy Self−HPV/colpo from 1.85 to 5.74
strategy Self−HPV/PAP from 2.06 to 6.07
strategy PAP/HPV from 3.48 to 8.79,

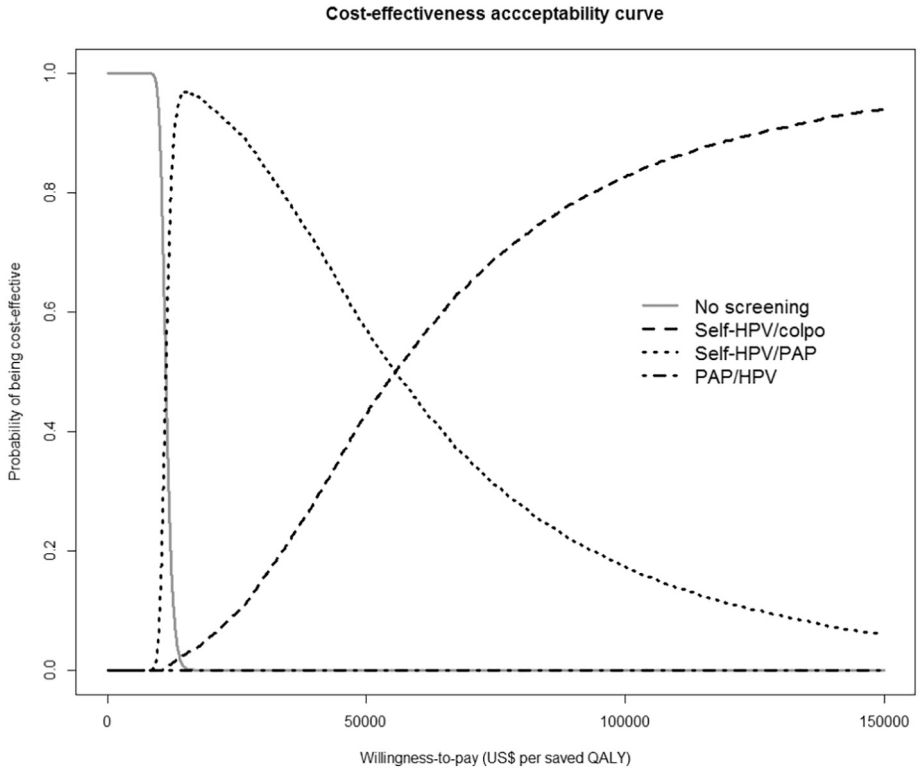

Fig. 2. Cost-effectiveness acceptability curve (CEAC). For a willingness-to-pay of 50,000 US$ per QALY, the estimated probability for the strategy Self-HPV/PAP to be cost-effective was 0.59.

and the CC related mortality (per 1000 women) was 4 times higher (ST4):

strategy Self−HPV/colpo from 0.55 to 2.33
strategy Self−HPV/PAP from 0.63 to 2.48
strategy PAP/HPV from 1.19 to 3.80.

The life expectancy was decreased by 0.05 years in Self-HPV/colpo and Self-HPV/PAP strategies (from 58.96 to 58.91) and by 0.07 years in the PAP/HPV strategy (ST5). Therefore, the cost related to CC (treatment, palliative care) increased while the cost related to the detection of cancer (tests, colposcopy) decreased (ST6). Since the average cost per woman decreased with the frequency of screening more importantly than the life expectancy, the ICER decreased when the frequency of screening increased. The ICER for a frequency of 10 years was (per saved QALY) (ST7):

strategy Self−HPV/colpo 5566 US
strategy Self−HPV/PAP5019 US strategy PAP/HPV 11, 569 US,

4. Discussion

This modeling study investigated the cost-effectiveness of three screening strategies, all of which were based on Self-HPV and PAP test, in unscreened women. As the cost of screening tests has been proven to be a barrier to CC screening participation, we assumed that screening attendance can be improved in this population when the cost of the tests is covered by the healthcare provider. The results of this study show that the screening program currently recommended in Switzerland (PAP/HPV) is cost-effective. However, the two strategies based on the Self-HPV test (with triage by colposcopy or by PAP) were found to be more efficient, less expensive and, therefore, more cost-effective than the PAP/HPV strategy. Based on these two strategies, a triage with colposcopy was more expensive than a triage with PAP, although the former had a small clinical benefit and, finally, led to an ICER higher than 50,000 US$ per QALY. Therefore, we found that the most cost-effective strategy in unscreened women was to offer Self-HPV tests with a triage by PAP. Compared to the lack of screening, this screening strategy would avoid 18.3 cases of CC per 1000 women and increase the life expectancy by 81 days.

These findings were robust across sensitivity analyses. The strategy HPV/PAP remained the most cost-effective for any compliance rate at each screening procedure from 50 to 90%. When the frequency of the screening procedure increased, the ICER decreased: this finding means that even if women participate in the screening program with a lower frequency than recommended, the strategy HPV/PAP was cost-effective. This can be explained by the higher sensitivity of HPV testing for the detection of cervical precancer than Pap testing. A negative result represents a great reassurance (low cancer risk), which permits screening at an extended interval of 5–10 years [26]. Despite these results, taking into consideration the fact that Switzerland uses an opportunistic screening we would advise a frequency of screening of 3 years [26].

Our analysis support studies stipulating that HPV-based screening strategies are more cost-effective than the strategy based on cytology screening alone. These studies were conducted in both high and low-income countries such as the Netherlands [27], UK [28], Iran [29], Thailand [30] and El Salvador [31]. These cost-effectiveness analyses, however, were performed on the general population. Our study focused on unscreened women, similarly to a French-population based randomized trial [32], which studied the cost-effectiveness of vaginal self-sampling as a means to increase participation in CC screening. This study showed an ICER per extra screened woman of 63.2 euros for the Self-HPV group relative to the control group [32]. Their analysis suggest that Self-HPV is cost-effective, although they do not investigate the impact in terms of life-expectancy and the analysis was solely based on the cost per extra screened woman. Our study reinforces their findings.

One strength of our study is that it reports the first economic evaluation of CC screening with HPV testing in Switzerland. We used data input from the most recent prospective studies. We also took into

account in our analysis the psychosocial impact of a positive HPV test or of an abnormal Pap test result.

Our study has some limitations that need to be addressed. Economic costs of routine follow-up visits after conization were included, but additional costs or health consequences associated with major adverse events resulting from treatment were not taken into account. For instance, preterm delivery resulting from conization might lead to important consequences of high economic impact associated with neonatal care. Another limitation is that we used HPV-testing starting at the age of 25 years. Some have suggested that HPV primary screening should start at the age of 30 years [33], but we focused on a specific population of women who do not participate in CC screening by offering a cost-effective test. Moreover, HPV vaccination was not taken into account. HPV vaccination may have an important impact in CC screening, especially concerning screening intervals. Finally, we applied a compliance rate at each screening procedure assuming that the compliance at a screening step is independent from the compliance with the previous one. Some women, however, may refuse to participate in CC screening throughout their whole life. We did not model this type of behavior due to the lack of data.

Our study focused on unscreened women. Unscreened women often come from lower socioeconomic groups or from immigrant minorities [34]. In Switzerland, immigrants comprise 24.6% of the population, which is one of the highest proportions of immigrants living in Western countries [35]. As the lack of screening participation among these groups of the population may be due to financial reasons, offering screening tests free of charge is an appropriate strategy to improve the compliance to screening. However, our findings suggest also that the Self-HPV test with a triage by PAP test would be a cost-effective alternative to the currently recommended screening (PAP test with a triage by HPV test) in the Swiss general population of women and may be of broad interest for other countries. Indeed, the cost of screening tests is lower with the Self-HPV test than with the PAP test, and life expectancy was also higher with the Self-HPV/PAP strategy than with the PAP/HPV strategy.

However, due to the opportunistic nature of screening in Switzerland, self-sampling for HPV primary screening should be implemented with careful consideration. The most recent Swiss guidelines [3] recommend primary HPV testing with a transition phase to facilitate the switch from cytology-based to HPV-based screening. The next step would be to adopt a national, organized screening program in order to ensure systematic screening and follow-up of abnormal results. Women's opinion and their concern over Self-HPV's accuracy should also be taken into account, and the possibility to have a physician-collected sample performed instead should be offered in selected cases. Self-HPV should also complement, and not replace women's healthcare services in order not to reduce patients' access to clinical assessment. In this context, this is an opportune time to incorporate Self-HPV as part of the national screening program to reach higher-risk women.

In conclusion, Self-HPV is a cost-effective option that could significantly reduce morbidity and mortality attributable to CC among unscreened women. For the recommended 3-year screening intervals, triage of HPV-positive women with a Pap test was the most cost-effective one.

Author contribution

PV designed the study, drafted the manuscript and finalized the work. AP and CC processed the experimental data, performed the analysis, drafted the manuscript and designed the figures and tables. RC and MV aided in interpreting the results and worked on the manuscript. PP and CC were involved in planning and supervised the work. All authors discussed the results and commented on the manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.01.021.

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