Effect of Type-Specific Human Papillomavirus Incidence on Screening Performance and Cost

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Background: Implementation of human papillomavirus (HPV) vaccination is expected to change the epidemiology of HPV infection.

Methods: Using age-dependent (inhomogeneous) Markov chains, we tested the effect of type-specific (ie, HPV-16/HPV-18 and other high-risk HPV types) HPV incidence on 3 screening strategies in a cohort of 100,000 women, starting screening at the age of 25 years and continuing until the age of 34 years. All the strategies started with an HPV test; if the result was positive, the next step was triage with cytology (strategy 1), cytology and colposcopy together (strategy 2), or colposcopy only (strategy 3). Published background data were used for the models.

Results: Strategy 2 had the highest sensitivity; the absolute number of missed cervical intraepithelial neoplasia (CIN)3+ cases was associated with HPV incidence in all the strategies, but their relative sensitivity remained unaffected. Strategy 2 was cheaper per diagnosed CIN3+ for very low HPV incidence rates, but this changed for higher incidence rates. For any given pair of HPV-16/HPV-18 and other high-risk–type incidence, the cost of the triage and the total cost of screening was highest in screening 2 and lowest in screening 1. For each screening strategy, the cost per diagnosed CIN3+ was mainly determined by the incidence of HPV-16/HPV-18, and the cost of the triage and the total screening cost by the incidence of other high-risk types.

Conclusions: Type-specific HPV incidence affects the absolute number of missed CIN3+ cases and the cost of screening in a mathematically describable way and can be used for prediction of changes in these outcomes with changing HPV epidemiology.

Key Words: HPV, Screening, Hybrid capture, Cytology, Colposcopy

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The recognition of human papillomavirus (HPV) infection as a necessary cause for virtually all cases of cervical cancer[1] and the identification of high-risk (HR) HPV types[2] during the last decade have resulted in the development of techniques for diagnosing current cervical infection and, more recently, in the development of prophylactic HPV vaccines.

Multiple studies have shown that HPV DNA testing is more sensitive than traditional cytology in detecting cervical intraepithelial neoplasia (CIN),[3–6] and the idea of HPV testing as the primary screening test is gaining momentum, with ongoing studies assessing potential different algorithms for the optimization of screening.

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Prophylactic HPV vaccine is expected to virtually completely protect against persistent infection and CIN caused by the type covered by it, and it will probably offer some degree of cross-protection against HPV-16– and HPV-18–related types[7–10] Moreover, routine vaccination of prepubertal and adolescent girls is expected to reduce the incidence of HPV infections in the overall by a percentage ranging between 12% and 95% 7 years after its implementation, depending on the coverage rate.[11] It is still unclear whether currently less common oncogenic types will compensate for the reduction in HPV-16/HPV-18 prevalence, changing thus further HPV distribution.

In view of the expected changes in HPV epidemiology, we designed the present study to test the effect of different rates of type-specific (ie, HPV-16/HPV-18 vs other HR types) HPV incidence on the clinical effectiveness and the selected cost estimates of cervical screening.

MATERIALS AND METHODS

We used age-dependent (inhomogeneous) Markov chains to test the effect of type-specific HPV incidence on the clinical effectiveness and the selected cost estimates of cervical screening. The Markov analysis allows embedding different screening policies on the natural history of the disease. In the present paper, we focused on 3 potential screening strategies based on HPV DNA testing.

Screening Strategies

All the strategies started with an HPV test (Fig. 1). If the HPV test result was negative, the women were seen in 3 years; if the HPV test result was positive, the next step was either triage with cytology (strategy 1, adapted from Cuzick et al[12]), cytology and colposcopy together (strategy 2, adapted from Ronco et al[13]), or colposcopy only (strategy 3).

Outcome Measures

The outcome measures for screening were the following:

1) Clinical effectiveness, defined by the total number of missed CIN3+ cases per 100,000 women at the end of the 10-year screening period.
2) Cost per diagnosed CIN3+ case.
3) Mean cost of triage per woman, defined as the cost of unnecessary tests (tests after an HPV test with a positive result in women screened at least once with positive HPV results and negative CIN2+ test results).

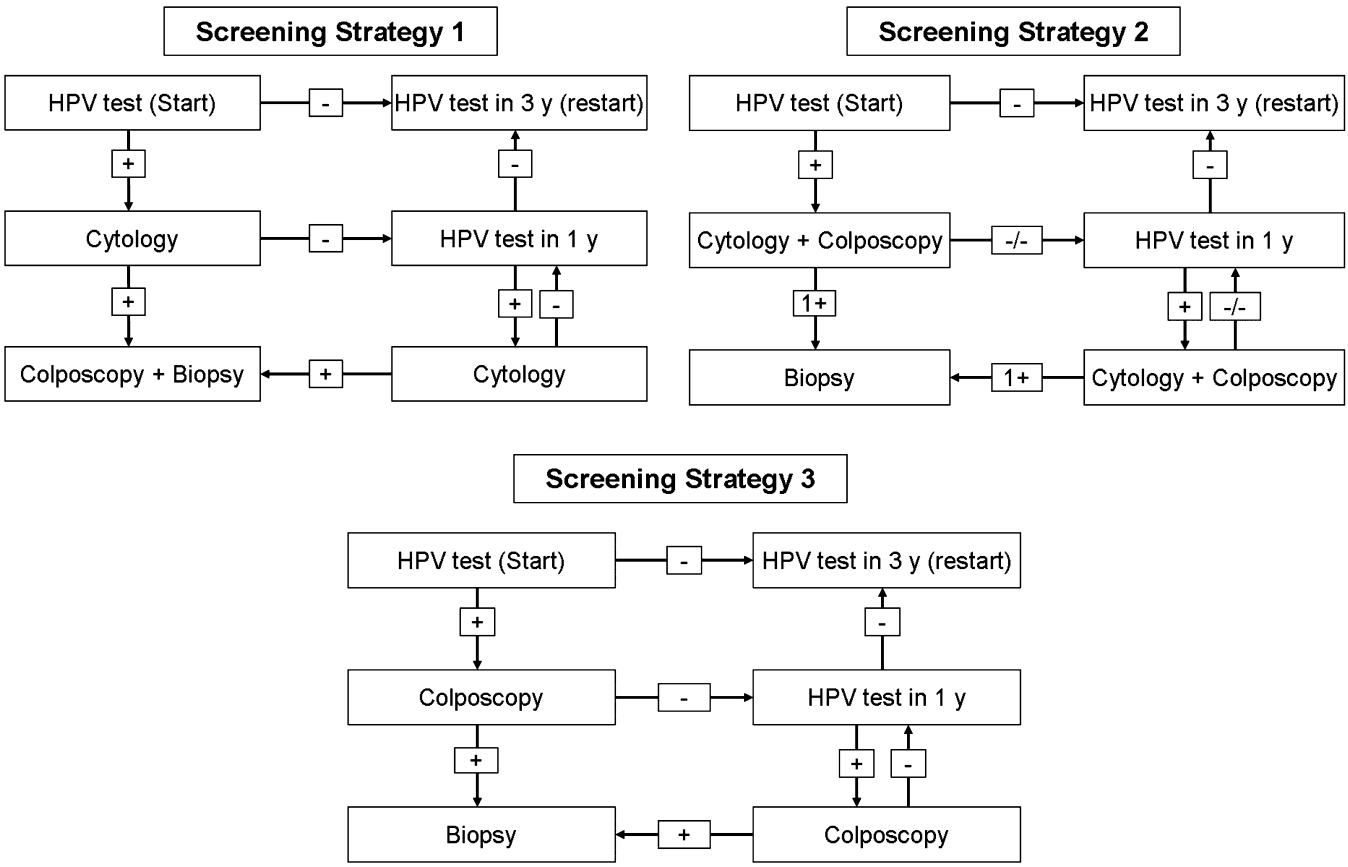

FIGURE 1. Schematic algorithm of the 3 screening strategies embedded on the natural history of HPV infection. Strategy 1, cytological triage after a positive HPV test; strategy 2, combined cytology and colposcopy after a positive pregnancy test; strategy 3, colposcopy alone for all women with a positive pregnancy test.

4) Total cost of screening (per 100,000 women at the end of the 10-year screening).

The costs of HPV DNA testing, cytology, colposcopy, and combined colposcopy plus biopsy were based on the weighted mean of 4 European countries.[14] Calculations were made for a discount rate of 3%.

Statistics: Modeling Methodology

Briefly, modeling involves 2 tasks: (*a*) the approximation of natural histories of HPV infection and cervical cancer and (*b*) the embedding of screening events into natural histories to assess the effectiveness of the alternative screening models.

Natural History of HPV Infection and Cervical Carcinogenesis. Closed (ie, fixed) cohorts of 100,000 initially noninfected women were created for different pairs of initial incidence rates of HPV-16/HPV-18 and other HR types, and they were followed up over a period of 13 years. For each cohort, we modeled the temporal development of HPV infection and cervical carcinogenesis as a stochastic first-order discrete-time Markov process with 6 mutually exclusive states (non–HPV infected, HPV-16/HPV-18 infected, other HR type infected, HPV-16/HPV-18 CIN2, other HR CIN2, and CIN3+). A figure illustrating the natural history of HPV infection used in the Markov model is given online (see Supplemental Digital Content 1, http://links.lww.com/IGC/A3). We chose to model the aggregate process directly instead of simulating individual life histories, as the former method has better computational efficiency and it is easily adaptable to a variety of screening strategies not considered here. In the present model, transitions between states occur at annual intervals, although different time intervals can be accommodated into the computational algorithm as needed per screening strategy. Transition probabilities for the development of HPV infection were assumed to be age specific. Individuals entered the process at the age of 22 years and were followed up through the age of 34 years. We tested for different pairs of initial incidence of HPV-16/HPV-18 and other HR types, which were calculated as follows: first, we sampled the HPV-16/HPV-18 incidence within the range 1.0% to 8.0% by equally spaced intervals of 0.25%. Then, for each HPV-16/HPV-18 incidence value, we used a step size of 0.5% to generate the incidence of other HR types accepting a range of values between 1.0 to 3.0 times that of the corresponding HPV-16/HPV-18 value, creating eventually 671 pairs of values.

Embedding the Screening Models. At each time step of the Markov process, the cohort was subjected to the 3 screening strategies. Screening began at the age of 25 years. The outcomes of screening were computed using published data about the characteristics (ie, sensitivity and specificity) of the tests involved.

Once each screening procedure was embedded in the infection process, the expected values of the system observables could be derived (1) at each time step and (2) at the end of the screening period. These include aggregates such as the number of cases with detected or undetected CIN3+, the time to CIN3+ detection, the number of specific tests performed, and the monetary cost of the screening strategies.

To assess the effects and relative importance of the HPV types' initial incidence rates on the costs of the 3 alternative strategies, we used the following regression equation (equation 1):

$$y_i = a_0 + a_1 x_{1i} + a_2 x_{2i} + \beta_1 \ln x_{1i} + \beta_2 \ln x_{2i} + \gamma_1 \frac{1}{x_{1i}} + \gamma_2 \frac{1}{x_{2i}} + \delta_1 x_{1i} x_{2i} + \delta_2 \ln x_{1i} \ln x_{2i} + \delta_3 \frac{1}{x_{1i}} \frac{1}{x_{2i}}$$

where i indicates observation, that is, a pair of HPV incidence values, (p_{12},p_{13}) and $x_1 = p_{12}$, $x_2 = p_{13}$; y is the cost variable; and a_0,a_1,a_2,β_1,β_2,γ_1,γ_2,δ_1,δ_2,δ_3 is the vector of regression parameters. Equation 1 is empirical, linear in the parameters, and an approximation of the true analytical relationship between cost and incidence rates. For all the cost variables, (*a*) all regression coefficients are statistically significant at the 1% level, (*b*) model diagnostics is supportive for the adopted model form of equation 1, and (*c*) the coefficient of determination of the regression, R^2, equals practically to 1, indicating a nearly perfect approximation of the true relationship within the range of incidence rates used.

TABLE 1. Transition rates and test performance estimators

Transition	Rate per Year
Well to HPV-16/HPV-18	Variable initial rate (modeling), changing with age
Well to other HR	Variable initial rate (modeling), changing with age
HPV-16/HPV-18 to well	50.0
HPV-16/HPV-18 to 16/18CIN2	8.2
HPV-16/HPV-18 to CIN3+	4.4 (women < 30 yr) and 6.0 (women ≥ 30 yr)
16/18CIN2 to CIN3+	12.5
16/18CIN2 to HPV-16/HPV-18	7.1
Other HR types to well	50.0
Other HR types to other HR CIN2	2.6
Other HR types to CIN3+	0.8
Other HR CIN2 to CIN3+	6.2
Other HR CIN2 to other HR HPV	14.2
Test/target	Sensitivity/false-positive rate
HPV test/HPV infection	96/0
Cytology/CIN2+	81/23
Colposcopy/CIN2+	85/31
Combined cytological screening + colposcopy	95/35

A full version of this table, complete with references, is provided online (see Supplemental Digital Content 2, http://links.lww.com/IGC/A4).

Assumptions

We accepted that all cases of cervical cancer arise from an HR-HPV infection and that all women targeted to be detected by screening (≥CIN2) have positive HR-HPV test results. The assumptions used in our modeling process are briefly presented in Table 1; a full version of the table, complete with references and a more detailed description on the assumptions, is provided online (see Supplemental Digital Content 2, http://links.lww.com/IGC/A4).

To simplify the model, we accepted CIN3+ as an end point, omitting the potential regression of CIN3 lesions and regarding it as a unified category together with carcinoma in situ and invasive cancer. This is based on the consensus that all lesions with CIN3 or higher should be diagnosed and treated. We have also dismissed the state of CIN1 because of its little clinical relevance. Finally, we pooled HPV-16 and HPV-18, despite their differing natural histories, because the implementation of prophylactic vaccination is expected to affect both in the same way.

Sensitivity Analyses

We have performed a sensitivity analysis for different sensitivities of the HPV test, the cytology, the colposcopy, and their combination. We tested the clinical effectiveness of the 3 strategies for HPV sensitivity ranging between 90.0% and 99.0%, cytological sensitivity ranging between 70.0% and 90.0%, colposcopic sensitivity ranging between 75.0% and 95.0%, and the sensitivity of their combination ranging between 80.0% and 99.0%.

RESULTS

Clinical Effectiveness

For each cycle of screening, the sensitivity for CIN2+ was 65.3% for strategy 1, 91.2% for strategy 2, and 81.6% for strategy 3. The cumulative percentages of CIN3+ cases missed at the end of the 10-year period of screening were 34.7% for model 1, 8.8% for model 2, and 18.4% for model 3, and this was independent of the incidence of type-specific HPV. However, the type-specific incidence of HR HPV infection affected the absolute number of CIN3+ cases missed at the end of the 10-year screening period as shown in Figure 2.

It the context of the sensitivity analysis, we calculated the overall performance of the 3 strategies (expressed as percent missed CIN3+ cases) for different sensitivity values of HPV testing (range, 0.90–0.99), cytology (range, 0.70–0.90), colposcopy (range, 0.75–0.95), and their combination (range, 0.80–0.99). For each screening strategy independently, the proportion of CIN3+ cases missed can vary between 15% and 53% (strategy 1), 2% and 28% (strategy 2), and 6% and 33% (screening 3). For comparison between strategies, we imposed the following logical constraints on the relationships between the test sensitivities: (1) common tests have identical sensitivities across strategies, and (2) the combination of cytology and colposcopy is more sensitive than either of the two. It was found that still strategy 2 (combined cytology and colposcopy) was the most

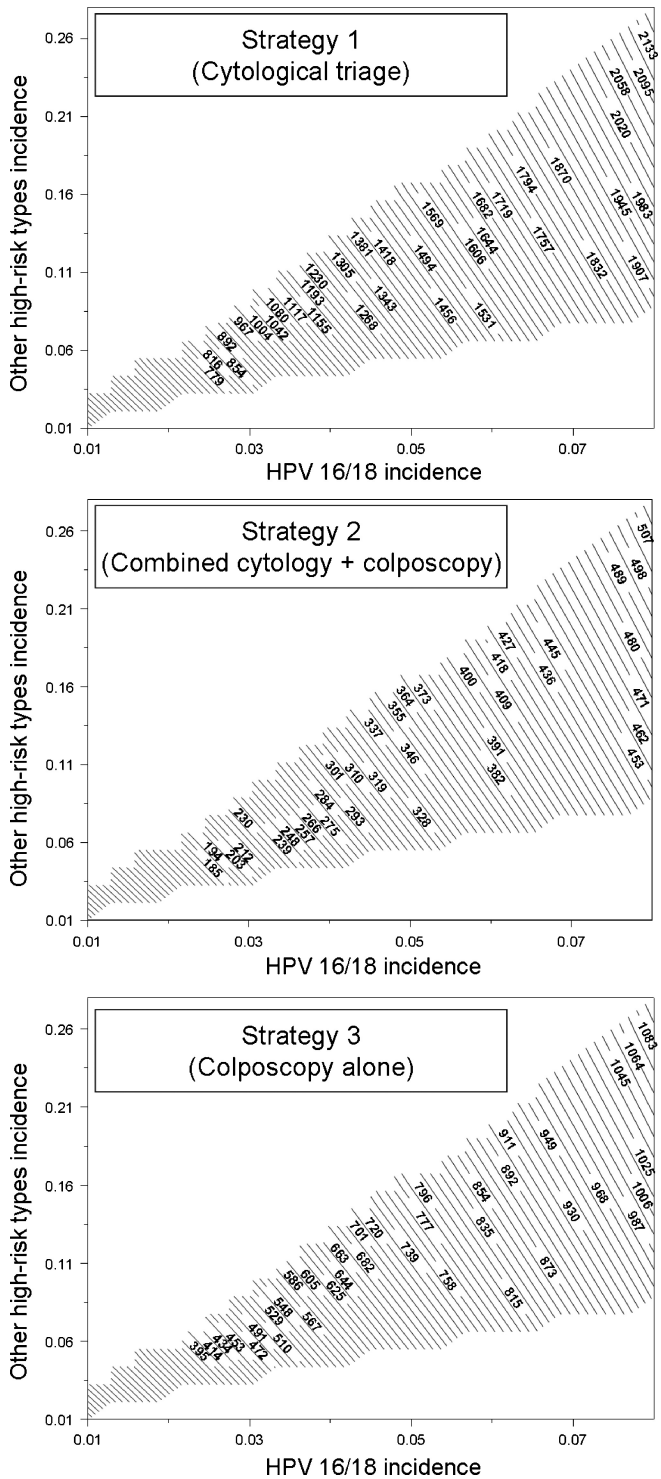

FIGURE 2. Contour plot for the effect of type-specific (ie, HPV-16/HPV-18 vs other HR types) HPV incidence on the number of missed CIN3+ cases. For each of the 3 screening strategies, the isolines show the cumulative number of missed CIN3+ cases per 100,000 women at the end of the 10-year screening period for the corresponding pairs of HPV-16/HPV-18 (*x*-axis) and other HR HPV (*y*-axis) incidences.

clinically effective policy, followed by strategy 3 (colposcopy alone) and then strategy 1 (cytological triage).

Cost Estimates

The cost per detected CIN3+ decreased with the increasing HPV incidence in all the 3 strategies tested. A figure illustrating the relationship between HPV incidence and cost per detected CIN3+ is provided online (see Supplemental Digital Content 3, http://links.lww.com/IGC/A5). Within each strategy, type-specific analysis showed that the incidence of HPV-16/HPV-18 is a more significant contributor than the incidence of other HR types for the cost per detected CIN3+.

The incidence of HPV infection was also found to affect the relative cost per detected CIN3+ in pairwise comparisons between the 3 strategies. More specifically, for very low rates of HPV infection, strategy 2 (combined colposcopy and cytology after a positive HPV test) was cheaper per detected CIN3+ than strategies 1 (cytological triage after a positive HPV test) and 3 (colposcopy alone after a positive HPV test), and strategy 3 was cheaper than strategy 1. These relationships were reversing with increasing HPV incidence rates. Figure 3 shows this transition for the comparison between strategies 1 and 2.

The cost of triage (cost of unnecessary tests after a positive HPV test in women having only HPV infection) was found to increase with increasing HPV incidence. A figure illustrating the relationship between HPV incidence and cost of triage is provided online (see Supplemental Digital Content 4, http://links.lww.com/IGC/A6). Within each strategy, type-specific analysis showed that the incidence of HR types other than HPV-16/HPV-18 was found to be a more significant contributor than the incidence of HPV-16/HPV-18 for the cost of triage. In contrast to the cost per detected CIN3+, the direction of cost differences in pairwise comparisons between the strategies did not change with changes in HPV incidence. Strategy 2 was always the more expensive; and strategy 1, the cheapest, with strategy 3 having an intermediate cost.

The total cost of screening also increased with the increasing incidence of HPV infection (Fig. 4). Again, in type-specific analysis, the incidence of HR types was found to be the major contributor for the total cost of screening.

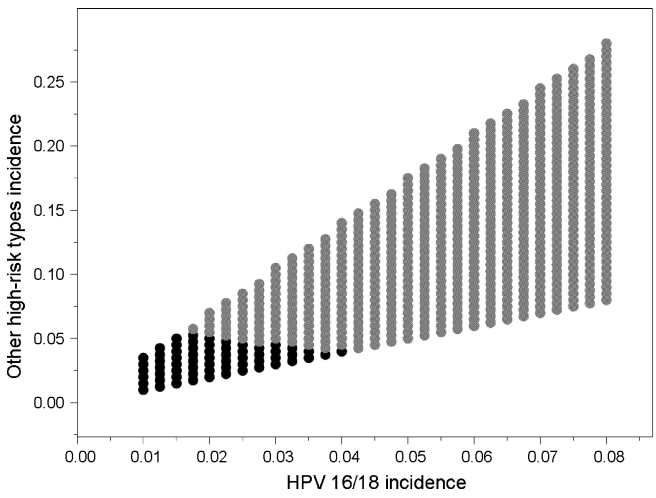

FIGURE 3. Effect of type-specific (ie, HPV-16/HPV-18 vs other HR types) HPV incidence on the cost difference per detected CIN3+ between strategies 1 (cytological triage after a positive pregnancy test) and 2 (combined colposcopy and cytology after a positive pregnancy test). The full dots represent areas of HPV incidence for which strategy 2 is cheaper than strategy 1 per detected CIN3+ case. The reversal of this relationship is marked by the transition to the shaded dot area.

DISCUSSION

Implementation of prophylactic vaccination is expected to bring about a significant change in HPV epidemiology, proportional to the extent of vaccination uptake. The aim of this study was to test the effect, if any, of changing HPV incidence rates on the clinical effectiveness (number of missed CIN3+ cases) and cost of screening.

We used age-dependent Markov chains to embed screening on the natural history of HPV infection. A strength of this approach is that any screening police can be fitted on the model; for practical reasons, we tested at present 3 potential strategies. In the first strategy, a positive HPV test is followed by a cytology, and if the result of the latter is positive, the woman is referred for colposcopy.[12] This approach is a very likely candidate for screening protocols, as it appears as the evolution of traditional cytology. The second strategy, that is, combined cytology and colposcopy after a positive HPV test, is a modification of the experimental algorithm used in the New Technology in Cervical Cancer study for women aged 35 years or older, which was found to be, overall, approximately 2 times more sensitive than traditional cytology.[6,13] The third screening strategy, that is, colposcopy alone for all women with a positive HPV test, is also a modification of the aforementioned New Technologies for Cervical Cancer strategy (women were referred to colposcopy if either the result of the HPV test was positive or the cytology result showed atypical squamous cells of undetermined significance or higher), with the omission of the cytological component based on the concept that any clinically significant atypical squamous cells of undetermined significance result should be HPV positive.

We found that:

1) Within each strategy, the absolute number of missed CIN3+ cases increased with increasing rates of HPV incidence, but the relative clinical effectiveness of the 3 strategies remained unaffected. The relative clinical effectiveness of the 3 strategies generally appeared robust for the sensitivity ranges tested. There was a substantial overlapping in the sensitivity of colposcopy alone and combined cytology with colposcopy in settings with very high sensitivity of screening colposcopy.
2) The cost per detected CIN3+ case decreased with increasing HPV incidence, and this happened in such a way that for very low HPV incidence rates, combined cytology and colposcopy (strategy 2) was cheaper per diagnosed CIN3+ case than the other 2 strategies, with this relationship reversing for higher HPV incidence.

3) The cost of triage and the total cost of screening increased with increasing HPV incidence.
4) For any given pair of HPV-16/HPV-18 and other HR-type incidences, the cost of triage and the total cost of screening were highest in strategy 2 (combined cytology and colposcopy after a positive HPV test) and lowest in strategy 1 (cytological triage), whereas strategy 3 (colposcopy alone) was in an intermediate position.
5) Regarding type-specific (ie, HPV-16/HPV-18 vs other HR types) incidence, HPV-16/HPV-18 was the major contributor of the cost per detected CIN3+, whereas the other HR types were the major contributor for the cost of triage and the total cost of screening.

Most of these results (eg, increasing number of missed CIN3+ cases with increased HPV incidence) were intuitively expected; however, our analysis provides the mathematic framework for the description of the relationship between HPV incidence and the studied outcomes, allowing prediction of screening behavior under different conditions of HPV infection. For example, for strategy 1 (cytological triage after a positive pregnancy test), a drop in HPV-16/HPV-18 incidence from 6% to 3% with a steady 8% incidence for other HR types would reduce the number of missed CIN3+ cases from 1530 to 1000 per 100,000 women per 10 years of screening (35% reduction), but the cost would only be reduced from $21.3 to $19.9 million (7% reduction). This example illustrates the degree by which HR types other than HPV-16/HPV-18 influence the total cost of screening both in financial burden and the corresponding unnecessary secondary tests, as long as the current approach with Hybrid Capture 2 testing is followed. This problem has been recently recognized, and it is sought to be addressed by typing the specific HPV strain, creating assays focusing on the highest-risk types, or testing for specific progression biomarkers of cervical carcinogenesis.[15] Our analysis framework is adaptable to the addition of such components, making it useful in the planning process of screening policies based on particular epidemiological features of the target group.

For the design of our analysis and given that the HPV epidemiology, the transition dynamics, and the medical history of the participants changes with age, we chose to commence HPV-based screening at the controversial age of 25 and simulate a decade of screening in a cohort of relatively young women, bypassing the large group of very young women with transient HPV infections, in whom the prevalence of CIN3+ is asymmetrically low compared with the high frequency of HPV infection.[16] Still, our model can be expanded in older women by modifying some of the underlying assumptions.

A shortcoming of our analysis, inherent indeed to modeling studies, is the introduction of some degree of oversimplification in the natural history of HPV infection.

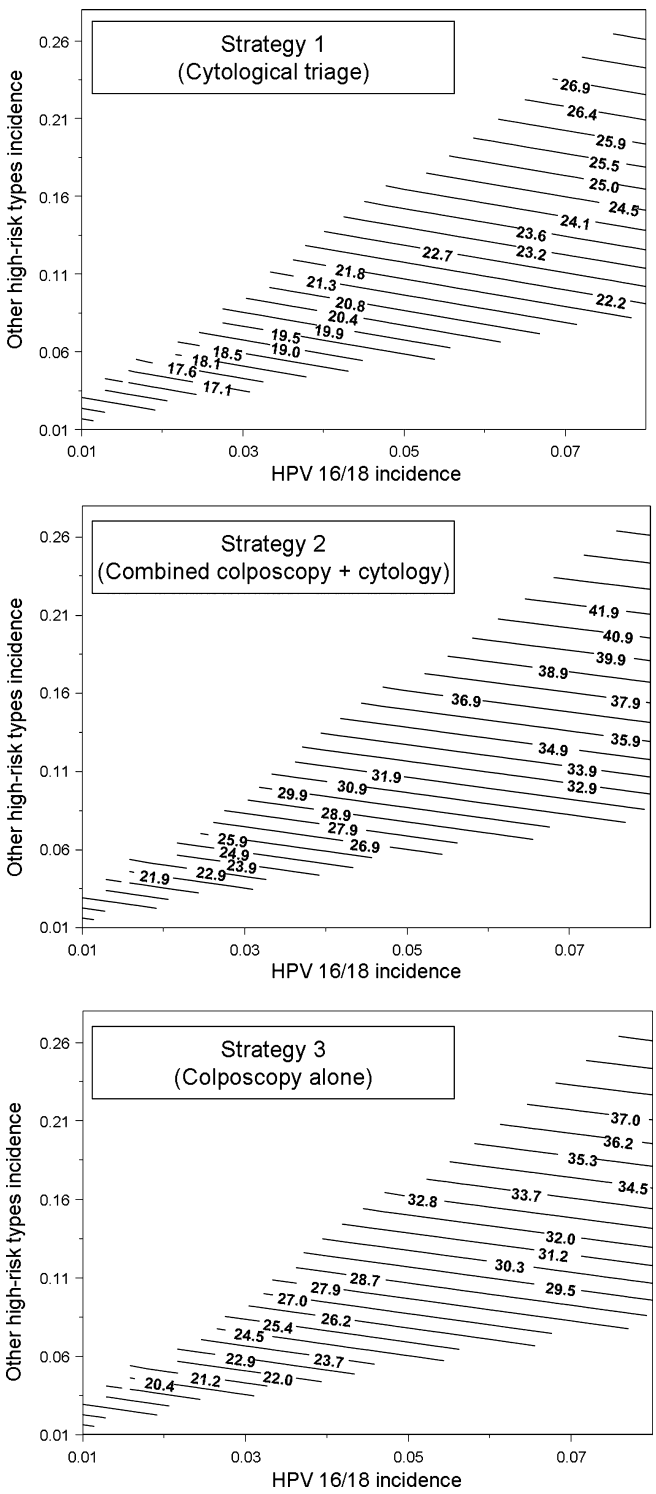

FIGURE 4. Contour plots for the effect of type-specific (ie, HPV-16/HPV-18 vs other HR types) HPV incidence on the total cost of screening, that is, the cumulative cost for the 100,000-women cohort at the end of the 10-year screening period. For each of the 3 screening strategies, the numbers in the isolines represent the mean cost of triage (in million US dollars) for the corresponding pairs of HPV-16/HPV-18 (*x*-axis) and other HR HPV (*y*-axis) incidences. The cost estimates for the tests were adapted from Kim et al[14] and were based on the weighted mean of 4 European countries, accepting a 3% annual discount rate.

Thus, we pooled the natural histories of HPV-16 and HPV-18, although they differ, because these 2 types represent the target of current HPV vaccines, which are expected to affect both in the same way. Similarly, we chose CIN3+ rather than cervical cancer as the screening outcome of interest, and we truncated the analysis at CIN3 based on the concept that CIN3+ should be detected and treated, together with the fact that cervical cancer prevalence in women younger than 35 years is very low.

Finally, as the aim of our analysis was to illustrate how changes in HPV incidence correlate with screening performance and selected cost estimates, we followed a limited cost analysis approach, similar to that of Coupe at al,[17] rather than performing a formal cost-effectiveness analysis, which would not be as intuitive and informative for the purposes of the present study.

In summary, it seems that of the 3 screening strategies tested, combined cytology and colposcopy after a positive HPV test is the most sensitive policy, missing the least CIN3+ cases. The type-specific HPV incidence affects the absolute number of missed CIN3+ cases, the cost of diagnosed CIN3+, the cost of triage, and the total cost of screening in a way that can be mathematically described and facilitates prediction of changes in these outcomes with changing HPV incidence rates.

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