Benefits and Costs of Using HPV Testing to Screen for Cervical Cancer

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Context Despite quality assurance standards, Papanicolaou (Pap) test characteristics remain less than optimal.

Objective To compare the societal costs and benefits of human papillomavirus (HPV) testing, Pap testing, and their combination to screen for cervical cancer.

Design, Setting, and Population A simulation model of neoplasia natural history was used to estimate the societal costs and quality-adjusted life expectancy associated with 18 different general population screening strategies: Pap plus HPV testing, Pap testing alone, and HPV testing alone every 2 or 3 years among hypothetical longitudinal cohorts of US women beginning at age 20 years and continuing to 65 years, 75 years, or death.

Main Outcome Measure Discounted costs per quality-adjusted life-year (QALY) saved of each screening strategy.

Results Maximal savings in lives were achieved by screening every 2 years until death with combined HPV and Pap testing at an incremental cost of $76 183 per QALY compared with Pap testing alone every 2 years. Stopping biennial screening with HPV and Pap testing at age 75 years captures 97.8% of the benefits of lifetime screening at a cost of $70 347 per QALY. Combined biennial HPV and Pap testing to age 65 years captures 86.6% of the benefits achievable by continuing to screen until age 75 years. Human papillomavirus screening alone was equally effective as Pap testing alone at any given screening interval or age of screening cessation but was more costly and therefore was dominated. In sensitivity analyses, HPV testing would be more effective and less costly than Pap testing at a cost threshold of $5 for an HPV test.

Conclusions Screening with HPV plus Pap tests every 2 years appears to save additional years of life at reasonable costs compared with Pap testing alone. Applying age limits to screening is a viable option to maintain benefits while reducing costs.

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THE INCIDENCE OF AND MORTALITY from cervical cancer have declined substantially in the United States over the last 4 decades.[1] These trends are largely attributed to the success of widespread Papanicolaou (Pap) smear screening programs. About 50 million Pap smears are performed annually in the United States.[2] Unfortunately, despite implementation of widespread quality assurance standards, Pap test characteristics remain less than optimal, with 25% to 50% false-negative rates.[3-5]

This potential for missing neoplasia has prompted the development of enhanced cytology-based technologies, such as automated rescreening of negative smears,[6,7] and alternative collection media.[8-10] While these new approaches appear to detect cases of neoplasia that might have been missed otherwise using conventional cytology, they may be too expensive to be a viable public health strategy.[5,11,12] Evolving understanding of the etiologic role of human papillomavirus (HPV) infection in cervical carcinogenesis[13,14] and advances in technologies for HPV detection have prompted exploration of HPV testing as an adjunct or primary screening tool.[15-26]

We used a mathematical model of the natural history of cervical cancer to estimate the incremental societal costs and benefits of screening in the average US population using HPV testing (alone or in combination with a Pap smear) compared with Pap smears alone.

See also pp 2382 and 2428 and Patient Page.

METHODS

We assumed that cervical cancer develops as the result of the progression of uncleared HPV infection to high-grade and eventually invasive disease.

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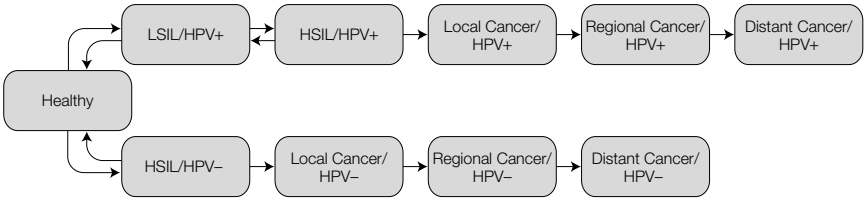
We developed a C++ program for a 17-state deterministic semi-Markov model[27] to portray the dynamic nature of cervical carcinogenesis (FIGURE 1). A second-order Monte Carlo stochastic simulation[27] was used to assess uncertainty. Each simulation represents a cohort of 1 million women, each moving through a 1-year cycle. All health states represent a pathologic state. Women may transition between states as a result of being screened, developing symptoms, having a hysterectomy for noncancer reasons, or dying from cervical cancer or other causes. They may also stay in the same state. The model "remembers" prior states once women are diagnosed with cancer and treated.

We used this model to estimate the societal costs and quality-adjusted life expectancy associated with 18 different general population screening strategies: joint Pap smear and HPV testing, Pap testing alone, and HPV testing alone every 2 or 3 years among hypothetical longitudinal cohorts of women beginning at age 20 years and continuing to either age 65 or 75 years, or death (ie, 3 strategies × 2 intervals × 3 ages of cessation). In sensitivity analyses we examined use of ThinPrep (Cytyc Corp, Boxborough, Mass), a newer technology that is just beginning to diffuse into practice.[11] We chose biennial and triennial intervals because these most closely reflect current professional guidelines and clinical practice. We examined different ages of cessation to inform screening policy.

In the joint Pap and HPV strategy, women were considered to have abnormal screening results if they had either a Pap smear indicating low-grade squamous intraepithelial lesion (LSIL) or a more pathologic result, a positive HPV test result, or both. Our analysis was restricted to women without HIV infection.[28-30] We did not include a "no screening" strategy because new interventions should be compared with current standards of care.[31]

We calculated incremental cost-effectiveness ratios in which the additional costs of a strategy, divided by the added savings in quality-adjusted life-years (QALYs) saved, were compared with the next least-expensive strategy.[31] We also calculated the number of tests performed and invasive cancers and deaths associated with each strategy. Investments in screening programs yield future savings in costs and lives. Discounting adjusts these future costs and outcomes to current values; we discounted all costs and effects at 3%.[31]

Figure 1. Representation of Model States



Each circle represents a health state. Not shown are states for human papillomavirus (HPV)-positive and HPV-negative local, regional, and distant cancers that are diagnosed and treated. LSIL indicates low-grade intraepithelial lesion; HSIL, high-grade intraepithelial lesion. Women may have a hysterectomy and no longer be at risk. At any time women can die of cervical cancer or any other cause.

Model Assumptions

There are several underlying assumptions in our model. The key assumption is that cervical neoplasia reflects the natural history of HPV infection and rarely (~5%) occurs in the absence of this infection.[13,14,32-34] To produce a model that reflects the underlying events in cervical neoplasia, yet is parsimonious, we also made several simplifying assumptions. First, we combined the state for newly acquired HPV infection (with or without cytological or histological abnormalities) and LSILs (cytological and pathological evidence of HPV infection or neoplasia) into one state. We made this decision because the transition between these states and back to "healthy" is very rapid and frequent and there are limited reliable primary data to quantify these probabilities and also because the reproducibility of interpretations of these states is only fair, leading to high potential for misclassification.[35]

Next, since atypical squamous cells of uncertain significance (ASCUS) is a cytologic finding and not a pathological state, we considered ASCUS to be a negative test result. All model sensitivity and specificity values reflect this cut point. This assumption results in a conservative estimate of the sensitivity of the Pap smear. We assumed that women will return to screening in the next interval and will not have colposcopy until (and if) they develop HPV/LSIL. However, if women have an ASCUS result and a positive HPV result in the combination strategies, they receive colposcopy. We examined alternative assumptions about ASCUS cut-point and workup costs in sensitivity analyses.[5]

Third, while women treated for HPV/LSIL may have either a higher or lower probability of redeveloping HPV/LSIL after treatment, the model Markov states do not have the ability to "remember" prior events.[36] Thus, we assumed that women treated for HPV/LSIL and cured return to "healthy" and acquire new HPV infection at similar rates to women without prior HPV/LSIL; women treated and not cured remain in the HPV/LSIL state. Finally, we made the simplifying assumption that HPV and Pap smear results are conditionally independent (ie, the results of one do not affect results of the other).[37]

Model Parameters

To estimate the probability (and costs) of all events in the model, we abstracted data from the best-quality published studies. Parameters are summarized in TABLES 1 and 2.[38-95]

Disease Natural History

Our general approach to modeling the disease course was to begin with ob-

Table 1. Model Effect Parameters*

Parameter	Base Case (Range)
Disease Natural History	
Prevalence of HPV/LSIL by age, y[19,38-54]†	
20-24	0.245
≥75	0.009
Transition probabilities‡§	
Progression from healthy to HPV/LSIL by age, y[5]	
20-65	0.225-0.284
Regression from HPV/LSIL to healthy§	0.284
Persistence of HPV/LSIL[20,55-60]	([1−{Regression + progression}] × [1-competing mortality])
Progression from HPV/LSIL to HSIL by age, y[20,55,57,59-71]	
20-65	0.010-0.079
Regression from HSIL to HPV/LSIL by age, y[19,59,68,69]	
20-74	0.250
≥75	0.196
Persistence of HSIL[19,63]	([1−{Regression + progression}] × [1−competing mortality])
Progression from HSIL to invasive cancer by age, y[19,59,68,69]	
20-65	0.011-0.057
Screening and Diagnostic Test Characteristics	
Pap smear (ASCUS as negative)[3-5,11,28,52,72-75]	
Sensitivity, %, for LSIL	62 (47-75)
<55 y	75
≥55 y	47
Sensitivity, %, for ≥HSIL	78 (61-84)
<55 y	84
≥55 y	61
Specificity, %, for ≥LSIL	90 (69-97)
<55 y	97
≥55 y	69
Pap smear (ASCUS positive cut point)[3-5,11,28,52,72-75]	
Sensitivity for LSIL, %	67
Sensitivity for ≥HSIL, %	80
Specificity, %	87
Pap smear (Thin Prep)[3-5,11,28,52,72-75]	
Sensitivity for LSIL, %	70
Sensitivity for ≥HSIL, %	88
Specificity, %	89
HPV DNA testing with Hybrid Capture II/PCR[23,47,70,76-81]	
Sensitivity, %, for LSIL	55 (43-70)
<55 y	43
≥55 y	70
Sensitivity, %, for ≥HSIL	89 (63-95)
<55 y	63
≥55 y	95
Screening and Diagnostic Test Characteristics (cont)	
Specificity, %, for ≥LSIL	86 (80-95)
<55 y	80
≥55 y	95
Sensitivity in HPV-negative HSIL/invasive cancer	1−Specificity
Colposcopy and biopsy (with endocervical curettage as needed)[23,47,70,76-81]	
Sensitivity, %, for ≥LSIL	100
Specificity, %, for ≥LSIL	100
Cure Rates for Preinvasive Disease, %[82]	
LSIL: cryotherapy or LEEP	95 (85-98)
HSIL: hysterectomy or cone biopsy	98 (90-99)
Compliance, %[83]	
Screening	
<70 y	80 (10-100)
≥70 y	58.7 (10-100)
Diagnosis	100 (10-100)
Treatment	100 (10-100)
Age-Specific 5-Year Survival‡	
Local invasive by age, y[84]	
All ages	0.875
19-24	0.976
≥75	0.764
Regional invasive by age, y[84]	
All ages	0.436
19-24	0.400
≥75	0.214
Distant invasive by age, y[84]	
All ages	0.079
19-24	0.071
≥75	0.032
Age- and sex-specific average annual all-cause mortality by age, y[85]	
20-24	0.0005
≥85	0.147
Improvements in Survival Associated With Chemotherapy, RR of Death (95% CI)[86-88]	
Local disease	0.54 (0.34-0.86)
Regional and distant disease	0.58 (0.40-0.81)
Utilities for Quality-Adjusted Survival[89]	
False-positive	0.97
LSIL	0.97
HSIL	0.93
Local	0.90
Regional	0.70
Distant	0.50

*HPV indicates human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; Pap, Papanicolaou; ASCUS, atypical squamous cells of undetermined significance; PCR, polymerase chain reaction; LEEP, loop electrosurgical excision procedure; RR, relative risk; and CI, confidence interval.
†Calculated in 5-year age categories; only extreme values are shown.
‡All transition probabilities noted in the table are multiplied by (1−annual probability of death), so that total probability of movement between possible states is always equal to 1. Probabilities are based on observed data and then calibrated to produce observed cancer incidence rates.
§Data were imputed.

served cross-sectional rates of HPV infection. These data were then used with longitudinal data on the rates of progression, regression, and persistence of HPV infection to develop transition probabilities between states and to calculate incidence of new HPV infection.[96] Transition rates were assumed to be age-dependent based on biologically theorized disease natural history data.

Age-Specific Prevalence Rates. We estimated the weighted prevalence rates of oncogenic HPV/LSIL determined by polymerase chain reaction (PCR) or Hybrid Capture II (Digene Corp, Gaithersburg, Md) and performed in 1990 or later by pooling data from the United States, Scandinavia, and western European and some South American countries[19,38-54] using standard fixed effects meta-analytic methods. Data were fit to a declining exponential function using linear regression to predict the natural log transformation of prevalence.

Transition Probabilities. Transition rates for oncogenic HPV were calculated using pooled, weighted data from studies published between 1990 and 2000.[5,19,20,55-71] Pooled rates were converted to annual transition probabilities, calibrated in the model using current screening and detection rates[83] to predict intermediate events, and constrained so that the sum of the probability of all transitions and death from noncervical cancer equaled one. To accurately predict observed cancer rates, we used age-dependent transition probabilities (eg, regression is less likely in older than younger women).[58,68,97-100] Finally, once women develop invasive cancer disease does not regress, and in the absence of screening, these women present with clinical symptoms (10% symptomatic at local disease, 50% at regional, and 70% at distant).[5,72,100]

Test Characteristics

We include data on a range of sensitivity and specificity values of screening tests from studies with colposcopy and/or histological confirmation of disease status for all women testing positive and a reasonable proportion

testing negative.[4,101-104] In sensitivity analyses, we assumed that Pap[105,106] and HPV[58,70,80,81,107] screening performance varies by age.

Pap Smears. We pooled data on Pap smear performance in the United States and similar settings to estimate sensitivity for detecting LSIL (62%) and high-grade squamous intraepithelial lesion (HSIL) or invasive cancer (78%). We used one specificity estimate for lesions LSIL grade or higher (90%).[3-5,11,28,52,72-75]

HPV DNA Testing. Estimates of HPV test performance were calculated using summary receiver operating characteristic curve methods[4,108] and data from studies in the United States and developed countries that used PCR[34] or Hybrid Capture II[109,110] to detect oncogenic HPV.[23,47,70,76-81]

Diagnostic Evaluation

All women with abnormal screening results are referred for colposcopy and biopsy (and endocervical curettage, if the transformation zone is not fully visualized). Women with invasive cancer undergo staging, including a pelvic examination under anesthesia, chest radiography, and/or intravenous pyelography, computed tomography, or magnetic resonance imaging.[95]

Compliance

In our base case, we examined results of the alternative screening strategies given current US screening rates (average, 80%).[83] We assumed that all women comply with diagnostic evaluation and treatment once they have a positive screening result; alternative assumptions were tested in sensitivity analyses.

Treatment

Women diagnosed with LSIL undergo cryosurgery, laser surgery, or loop electrosurgical excision procedure (LEEP); we assumed that 95% (range, 85%-98%) would be cured. Women with LSIL receive close 5-year surveillance (every 3 months in year 1, every 6 months in year 2, and annually in years 3-5) and then return to routine screening. We assumed that future performance of Pap smears is independent of LSIL treatment. Women diagnosed with HSIL undergo a cone biopsy or a simple hysterectomy and 5-year surveillance; we assumed that 98% (range, 90%-99%) would be cured.[72,111-113] If women are diagnosed with local-stage invasive cancer, we assumed that they receive intracavitary radiation or a radical hysterectomy. Women diagnosed with regional and distant disease undergo radical hysterectomy and a course of external pelvic radiation. Women with invasive disease undergo close 5-year surveillance, then less inten-

Table 2. Medical Care Costs*

Cost	Base Case (Range), $
Screening Test Costs	
Pap smear[5,11,28,72,90-92,115]	
Initial office visit	47
Laboratory fee	10
Total	**57** (44-65)
ThinPrep	10
HPV test[28]	
Office visit	47
Laboratory fee	
Hybrid Capture II	30 (12-80)
PCR	77
Diagnosis	
Diagnostic evaluation for LSIL[5,28,72,90,91,99]	
Repeat Pap	57
Colposcopy + cervical biopsy + endocervical curettage	103
Extended office visit	108
Total	**268** (133-418)
Diagnostic evaluation for HSIL[5,28,72,90,91]‡	
Repeat Pap	57
Colposcopy + cervical biopsy + endocervical curettage	103
Extended office visit	108
Staging (20% of HSIL and 100% of invasive)	162
Total	**516** (432-583)
Initial treatment[5,28,72,90-92]‡	
LSIL (20% with cryotherapy, 20% with laser, 60% with LEEP)	469 (325-646)
HSIL (50% with simple hysterectomy; 50% with cone biopsy)	7826 (5642-10 170)
Local (50% with internal radiotherapy; 50% with radical or simple hysterectomy)	14 619 (12 917-17 990)
Regional (100% with radical hysterectomy; 100% with external radiation)	20 792 (18 548-23 294)
Distant (80% with radical hysterectomy; 20% with pelvic exenteration and 100% with external radiation)	21 553 (18 867-25 259)
Chemotherapy	7529 (3045-15 484)
Diagnosis (cont)	
Continuing care‡	
LSIL (3 Pap smears and intermediate office visits in year 1; 2 in year 2; and 1 in years 3-5)	
Year 1	182 (170-193)
Year 2	121 (114-129)
Years 3-5	61 (57-64)
HSIL (same surveillance as LSIL)	
Year 1	354 (170-700)
Year 2	314 (114-700)
Years 3-5	274 (57-700)
Local	580 (474-689)
Regional	931 (201-2142)
Distant	2164 (451-3877)
Terminal care‡	
Local	21 240 (20 695-21 785
Regional	25 538 (24 972-26 104)
Distant	23 790 (23 298-24 282)
Patient time costs[5,28,91,93]	
Screening	15
Diagnostic evaluation	
LSIL	19
HSIL	50
Initial treatment	
LSIL	17
HSIL	282
Local	626
Regional	2299
Distant	2355
Continuing care	
Local	62
Regional	92
Distant	92
Terminal care	
Distant	878

*Costs are in year 2000 dollars, based on the Consumer Price Index for medical services (in medical care component) from the Bureau of Labor Statistics.[94] See Table 1 footnotes for expansion of abbreviations.
†Cisplatin, fluorouracil, or hydroxyurea.[86-88]
‡Source includes SEER-Medicare linked data from 1986-1998.

sive surveillance annually until death. Finally, chemotherapy has recently been shown to increase survival,[86-88] so in sensitivity analyses we evaluated chemotherapy use.

Life Expectancy

Age-, race-, and sex-specific average annual mortality rates were used to estimate life expectancy of all women in the model.[85] Excess mortality due to cervical cancer (ie, relative survival) was derived from Surveillance, Epidemiology, and End Results (SEER) data. We calculated quality-adjusted survival using the following estimates: 0.97 for being healthy or having LSIL, 0.93 for having HSIL, and 0.9, 0.7, and 0.5 for having local, regional, and distant invasive cancer, respectively, where 1.0 represents perfect health and 0 is death.[89] We did not consider the disutility for short-term events, such as undergoing evaluation for a false-positive test result.

Costs

We included medical care (consumable supplies, personnel, laboratory, and procedure costs) and nonmedical care (patient time costs) direct costs (Table 2). Where possible, we used cost data based on resource utilization[28,72,90,114] or microcosting.[5] Otherwise we used gross cost accounting methods.[11] All costs were converted to constant year 2000 dollars using the medical care component of the Consumer Price Index for the year of data collection.[94] Pap costs were derived from published sources.[5,11,28,72,90-92,115] The costs of HPV DNA testing were estimated by experts (written communication, M. Manos, K. Shah, T. Wright, and A. Lorincz, 2000) and from published sources.[28]

The costs of diagnosing LSIL and HSIL and treating LSIL were estimated from prior analyses.[5,28,72,90,91,99] Costs of treating HSIL were estimated from initial care costs in linked SEER-Medicare data. Invasive cancer costs were derived from cervical cancer–specific costs of diagnosis, initial treatment, and continuing and terminal care from linked SEER-Medicare data from 1986-1998 using the method described by Brown and Garber.[11] We assumed that Medicare reimbursements, based on the Medicare Resource Based Relative Value Scale, approximate societal costs.[116]

Nonmedical costs included patient time spent receiving screening, diagnosis, and treatment (estimated from prior research and clinical estimates[28]) and travel and waiting time (based on data from the National Health Interview Survey[93]). Costs were obtained by multiplying these times by median wage rates.[94] The costs of lost productivity are accounted for by decrements in utilities.

Sensitivity Analyses

To assess the robustness of model results, we conducted sensitivity analyses to examine the effects of varying uncertain parameters over reasonable ranges.

Model Validation and Evaluating Uncertainty

The face and clinical validity of the model was reviewed by a panel of scientific advisors. We developed this model for use in US screened populations and validated it against estimated rates of cervical cancer in unscreened

Table 3. Costs, Health Effects, and Cost-effectiveness (CE) of 18 Cervical Cancer Screening Strategies*

			Costs		Health Effects, No.†				
Strategy	Screening Frequency, y	Screening Cessation Age, y	Maximum No. of Screens	Cost, $	Cases	Deaths	QALYs Saved	Incremental CE Ratio, $	Result
No screening				5018	3382	1822	26.8666		
Pap	3	65	16	6804	1020	434	27.0175	11 835	Not CE
Pap	3	75	19	6833	817	305	27.02	11 830	Frontier
Pap	3	100	27	6851	750	253	27.0204	45 250	Not CE
HPV	3	65	16	6904	1009	418	27.0183	–41 529	Dominated
HPV	3	75	19	6941	800	284	27.0209	119 644	Not CE
HPV	3	100	27	6964	729	229	27.0213	100 869	Not CE
Pap	2	65	16	7230	796	352	27.0315	34 529	Not CE
Pap	2	75	19	7280	523	185	27.035	29 781	Frontier
Pap	2	100	27	7308	437	124	27.0355	56 440	Frontier
Pap + HPV	3	65	16	7348	749	319	27.0321	–11 871	Dominated
HPV	2	65	16	7388	792	348	27.0314	–19 615	Dominated
Pap + HPV	3	75	19	7393	525	182	27.0347	–106 525	Dominated
Pap + HPV	3	100	27	7422	450	127	27.0352	–381 467	Dominated
HPV	2	75	19	7452	515	177	27.035	–288 780	Dominated
HPV	2	100	27	7489	425	113	27.0356	1 810 900	Not CE
Pap + HPV	2	65	16	7857	607	285	27.0408	103 504	Not CE
Pap + HPV	2	75	19	7934	317	113	27.0444	70 347	Frontier
Pap + HPV	2	100	27	7980	225	51	27.045	76 183	Frontier

*Strategies are listed in order of increasing cost. QALY indicates quality-adjusted life-year; Pap, Papanicolaou test; and HPV, human papillomavirus test.
†Number of cases of invasive cancer and number of deaths are per 100 000 women.

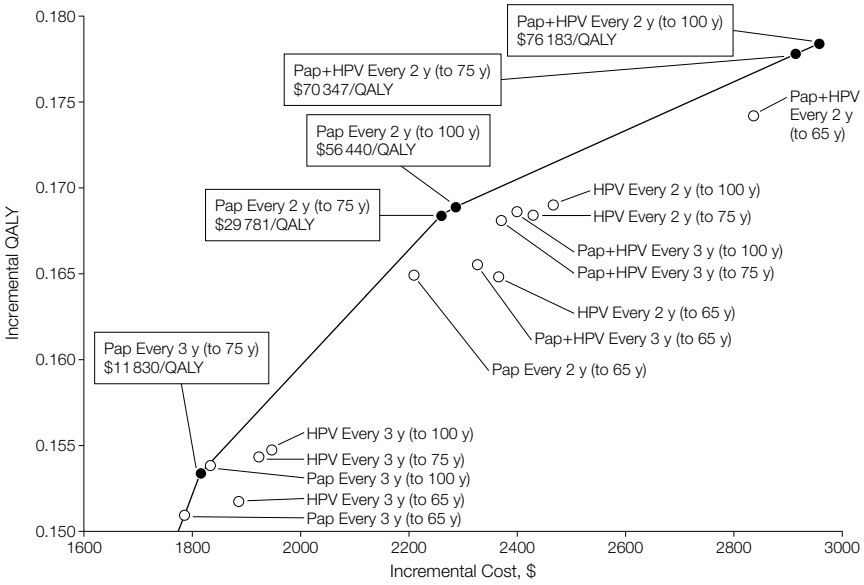
women.[5] We also examined the predictive ability of the model to use input on HPV rates from a different setting to predict observed cancer incidence rates.[117] We use a second-order Monte Carlo simulation[27] to examine uncertainty in parameters. The probability that strategies are cost-effective[118] was assessed using confidence intervals determined using bootstrap simulation[119] of replications of the cohort sample.

RESULTS

Without screening, the cumulative lifetime risk of invasive cervical cancer is 3.4%. Under baseline assumptions, all 18 screening strategies reduce cervical cancer incidence and mortality (TABLE 3). Comparing each strategy to the next most-effective nondominated option, the maximal savings in life years is achieved by screening every 2 years without an upper age limit (lifetime) using combined HPV and Pap tests at a cost of $76 183 per QALY saved (FIGURE 2). Adding HPV testing to lifetime biennial Pap screening saves an additional 3.5 days of discounted quality-adjusted life expectancy per woman (13.7 undiscounted days), avoids 225 invasive cancers per 100 000 women, and decreases cervical cancer mortality by an additional 59%. Compared with lifetime biennial Pap testing, 472 women would need to be screened biennially with HPV tests and Pap smears to avoid 1 case of invasive cancer and 1367 would need to be screened to avoid 1 death.

Biennial Pap tests from age 20 years to death generate 2.7 million colposcopies for a cohort of 1 million women (1.4 million of which will be falsely positive). Adding HPV testing increases this number to 4.7 million (with 3.2 million falsely positive). Strategies using HPV screening alone are generally dominated (ie, save fewer lives and cost more) by the other approaches. In the base case, strategies using HPV screening alone were generally equally effective as Pap smear alone at any given frequency of screening but were more expensive and therefore were dominated. The additional cost of HPV screening and its marginally lower specificity increase costs without additional effectiveness.

Figure 2. Incremental Cost-effectiveness (Efficiency Frontier) of 18 Screening Strategies



Strategies are labeled by the type and frequency of screening and the age of screening cessation (noted in parentheses). Pap indicates Papanicolaou test; HPV, human papillomavirus screening; and QALY, quality-adjusted life-year. Open circles represent strategies that are less cost-effective or cost more and save fewer QALYs than strategies on the efficiency frontier (closed circles). Cost-effectiveness data on the slope represent the comparison with the next most-effective option.

Discontinuing biennial screening with HPV and Pap testing at age 75 years captures 97.8% of the benefits of lifetime screening at a cost of $70 347 per QALY saved. Combined biennial HPV and Pap testing to age 65 years captures 86.6% of the benefits achievable by continuing to screen until age 75 years.

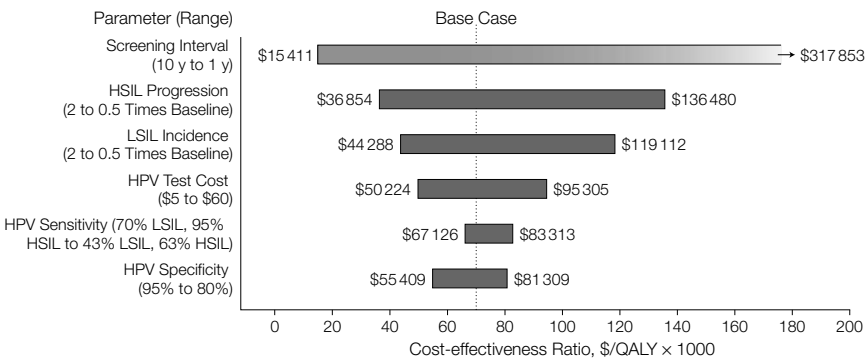
If the goal is to maintain a triennial screening schedule, among the 9 triennial strategies, combined Pap and HPV testing up to age 75 years is a very cost-effective strategy, costing $38 699 per QALY saved compared with triennial Pap screening to age 75 years.

Sensitivity Analyses

Changes in several variables alter the relative ranking of strategies, while variations in the remainder change the dollar amounts but not the conclusions. Assumptions about HPV test costs, sensitivity of HPV testing, and LSIL prevalence affect conclusions about the most cost-effective approaches. As HPV test costs decrease from $30 to $10, the absolute cost-effectiveness ratio for combined biennial screening decreases but its ranking relative to other strategies remains the same. However, as the costs decrease below this threshold to $5, then using HPV testing alone to age 100 years as a primary biennial screening approach becomes cost-effective (at approximately $50 100 per QALY saved) compared with HPV testing alone to age 75 years and dominates biennial Pap screening to age 100 years. Combined testing is also cost-effective to age 100 years at $65 100 compared with combined testing stopped at age 75 years.

Changes in test sensitivity may alter the conclusions about the optimal age of screening cessation. For instance, if HPV sensitivity improves to 85% at unchanged test specificity, more cases will be detected at earlier ages using biennially combined HPV and Pap testing, and the gains of continuing to screen after age 75 years are very small, so that combined biennial screening to age 75

Figure 3. One-Way Sensitivity Analysis



Analyses of the incremental cost-effectiveness ratio of Pap plus HPV testing compared with Pap testing alone. All analyses assume lifetime biennial testing from age 20 years to death. The vertical dotted line represents the base case ($76 183). See the legend to Figure 2 for definitions of abbreviations.

years now costs $66 703 per QALY saved compared with biennial Pap testing to age 100 years. Continuing to screen with HPV alone with an upper limit becomes fairly expensive ($93 100 per QALY saved) compared with stopping at age 75 years.

If the prevalence of HPV/LSIL doubles, the absolute cost-effectiveness ratio of combined HPV- and Pap-based strategies decreases, but the ranking relative to other strategies remains unchanged. However, if screening is applied in a population with half the baseline rates of HPV/LSIL, then combined lifetime biennial screening becomes very expensive (approximately $118 000 per QALY saved vs biennial Pap testing to age 100 years). In this setting, biennial screening with Pap smears alone to age 75 years would be the preferred strategy (with costs per QALY saved of $26 511 vs stopping at age 65 years and $92 000 for stopping at age 100 vs 75 years).

The absolute value of the cost-effectiveness results, but not the relative position of the different screening strategies (FIGURE 3), is affected by assumptions about the population screening rates, progression rates, whether HPV/LSIL lesions are treated, defining ASCUS as a positive Pap result, and using liquid-based cytology media. The results are not sensitive to assumptions about the proportion of HPV-negative cancers, HSIL treatment costs, chemotherapy use and costs, patient time costs, age dependence of test characteristics, or utilities (data not shown).

If we consider ASCUS as a positive result (increased sensitivity but decreased specificity), with increased evaluation costs, the cost-effectiveness ratio of combined lifetime biennial screening increases to $79 470 compared with using Pap testing alone. If liquid-based cytology is used to collect cells for Pap smears (and HPV tests), the costs of screening increase in all 18 strategies in proportion to increases in life expectancy due to improved sensitivity.

COMMENT

Using a comprehensive simulation model of the natural history of HPV-driven cervical carcinogenesis, we found that comparing each strategy to the next least-expensive option, maximal savings in life could be achieved by screening every 2 years from age 20 to death with a combination of HPV and Pap tests. Cessation of screening at age 65 or 75 years is less expensive and captures 86.6% and 97.8% of the benefits of lifetime biennial screening, respectively.

Pap results have been noted to have low sensitivity,[4] poor reproducibility, and high potential for misclassification.[35] Thus, parallel screening with cytology and HPV testing improves outcomes by increasing sensitivity (without major concomitant decrease in specificity),[120] where the additional savings in life-years are achieved at a reasonable incremental cost.

At a threshold of $5 per test, using HPV alone as a primary biennial screening approach becomes cost-effective and dominates biennial Pap screening. Since HPV testing requires minimal resources for materials and laboratory technicians, this $5 cost is within the realm of possibility. Pap smears, in contrast, require greater laboratory processing, cytotechnician training and staffing, and quality assurance maintenance. Pap smears, which have been on the market for several decades, are currently offered at levels equal to production costs and are not likely to become less expensive. The combination of low HPV cost, targeting to high-prevalence groups, and/or improved sensitivity would favor HPV as a primary screening strategy. This conclusion is consistent with the findings of other studies modeling the use of HPV as a primary screening test.[14,49,99,121-123]

Overall, HPV testing has several advantages as a primary screening strategy, including equivalent or higher sensitivity than Pap smears, ability to predict women at high risk for future disease, lower technician skill level than cytology, and having the potential for self-collection.[24,124-126] Assuming that testing for a sexually transmitted disease will be acceptable to the target population,[2] and that HPV tests could be provided at low cost, primary screening with HPV could be an excellent alternative to cytology in populations with high incidence of disease[1,106,127] or in less developed countries.[124,125]

The combination of biennial HPV and Pap tests avoids the greatest number of invasive cervical cancer cases and deaths. However, this progress is achieved at the expense of increasing the risk of undergoing colposcopy for evaluation of false-positive results. Since the positive predictive value of a positive HPV result is lower for younger vs older women,[58,121] younger women will

be more likely than older women to undergo colposcopy and therapy to evaluate (and treat) HPV infections that may have spontaneously regressed.

There is no consensus regarding the age of screening cessation.[74,128-130] In our analysis, lifetime screening continues to save lives, but virtually all of the benefits can be achieved by screening up until ages 65 to 75 years. Beyond this, the benefits are very small and must be weighed against the harms. For example, Sawaya et al[131] note that the probability of a false-positive Pap result is much greater than a true-positive result after age 65 years. However, if a woman has not been tested, screening remains indicated.

Our results are consistent with prior analyses that suggest that screening is reasonably cost-effective when performed every 2 or 3 years.[5,75,100,132] In our and other analyses, annual screening saves marginally more lives at extremely high costs.[5,75,132] For longer intervals, while costs are lower, the number of cases that may be missed could be unacceptably high.

Currently, the optimal diagnostic[35] and management approach to ASCUS Pap results[133] is still under study.[134] If all women with an ASCUS result receive diagnostic colposcopy, then our base results underestimate the costs of Pap screening. If women with ASCUS are triaged using HPV results as a guide, the number of colposcopies may be reduced at a modest cost. This is an important area for future analyses.

Our analysis has several important strengths, including use of current standards for cost-effectiveness analyses,[31] use of the best-quality and least-biased data, a robust, validated model, multiple screening strategies, and assessment of uncertainty. Our results are also comparable to and extend prior analyses.[5,100,132]

Despite these strengths, there are several limitations to our results, such as infrastructure issues, model assumptions, choice of technologies, short-term disutility, use of modeling, and generalizability. Our model assumes that screening occurs in an existing system and does not include infrastructure development costs. However, the costs of initiating and maintaining HPV laboratories are likely to be comparable to or lower than costs for cytology.

Our model combines HPV infection and LSIL into one state. While this simplification allowed us to use the most accurate natural history data available, it biases the results to make HPV screening appear slightly less favorable (due to higher rates of workup of transient HPV infection) relative to Pap screening. Other analysts have estimated transitions between HPV infection and LSIL by back-calculating for each state from transitions later in the course of disease to match observed events.[5,28,96] Since our model is calibrated to similar rates of observed events, our model should yield equivalent results.[5,28]

Regardless of modality chosen, the greatest health gains from screening will depend on reaching all women and ensuring access to diagnosis after an abnormal screening result (and treatment, if malignant).[100,135]

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