Trade-offs in Cervical Cancer Prevention

Balancing Benefits and Risks

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Background: New screening and vaccination technologies will provide women with more options for cervical cancer prevention. Because the risk of cervical cancer diminishes with effective routine screening, women may wish to consider additional attributes, such as the likelihood of false-positive results and diagnostic procedures for mild abnormalities likely to resolve without intervention in their screening choices.

Methods: We used an empirically calibrated simulation model of cervical cancer in the United States to assess the benefits and potential risks associated with prevention strategies differing by primary screening test, triage test for abnormal results (cytologic testing, human papillomavirus [HPV] DNA test), and screening frequency. Outcomes included colposcopy referrals, cervical intraepithelial neoplasia (CIN) types 1 and 2 or 3, lifetime cancer risk, and quality-adjusted life expectancy.

Results: Across strategies, colposcopy referrals and diagnostic workups varied 3-fold, although diagnostic rates of CIN 2 or 3 were similar and 95% of positive screening test results were for mild abnormalities likely to resolve on their own. For a representative group of a thousand 20-year-old women undergoing triennial screening for 10 years, we expect 1038 colposcopy referrals (7 CIN 2 or 3 diagnoses) from combined cytologic and HPV DNA testing and fewer than 200 referrals (6-7 CIN 2 or 3 diagnoses) for strategies that use triage testing. Similarly, for a thousand 40-year-old women, combined cytologic and HPV DNA testing led to 489 referrals (9 CIN 2 or 3), whereas alternative strategies resulted in fewer than 150 referrals (7-8 CIN 2 or 3). Using cytologic testing followed by triage testing in younger women minimizes both diagnostic workups and positive HPV test results, whereas in older women diagnostic workups are minimized with HPV DNA testing followed by cytologic triage testing.

Conclusions: Clinically relevant information highlighting trade-offs among cervical cancer prevention strategies allows for inclusion of personal preferences into women's decision making about screening and provides additional dimensions to the construction of clinical guidelines.

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Routine screening with cervical cytologic testing is widely credited with reducing cervical cancer incidence through the early detection and treatment of high-grade cervical intraepithelial neoplasia (CIN). The long duration between initial infection with human papillomavirus (HPV), development of low-grade cervical abnormalities, and progression to high-grade disease allows for effective prevention of invasive cancer. Today, women in the United States have an average lifetime risk of 0.7%.[1] Guidelines have recommended using cytologic testing as the primary screening test at annual to triennial intervals, with HPV DNA testing (Hybrid Capture II; Digene, Gaithersburg, Maryland) as an option for triage of equivocal cytologic test results.[2-5] More recently, the combination of HPV DNA testing as a primary screening test with cytologic testing has been suggested as a reasonable alternative for primary screening in women older than 30 years.[3,4] As evidence of the improved sensitivity of HPV DNA testing for detecting high-grade CIN accumulates, recommendations for its use in screening are likely to further evolve. For example, primary screening using HPV DNA testing followed by cytologic testing in women who are HPV positive is currently being evaluated in trials.[6] How best to capitalize on the enhanced sensitivity of HPV DNA testing while minimizing false-positive results from its lower specificity is an important question to be addressed in upcoming screening guidelines.

In addition to new screening diagnostics, 2 prophylactic vaccines against HPV types 16 and 18, responsible for approximately 70% of cervical cancer, appear highly efficacious.[7,8] Current US recommendations for routine vaccination are for young adolescent girls who stand to receive the most benefit, with temporary catch-up programs up to the age of 26 years.[9,10] Although important discussions have ensued regarding screening for vaccinated girls, most women today will

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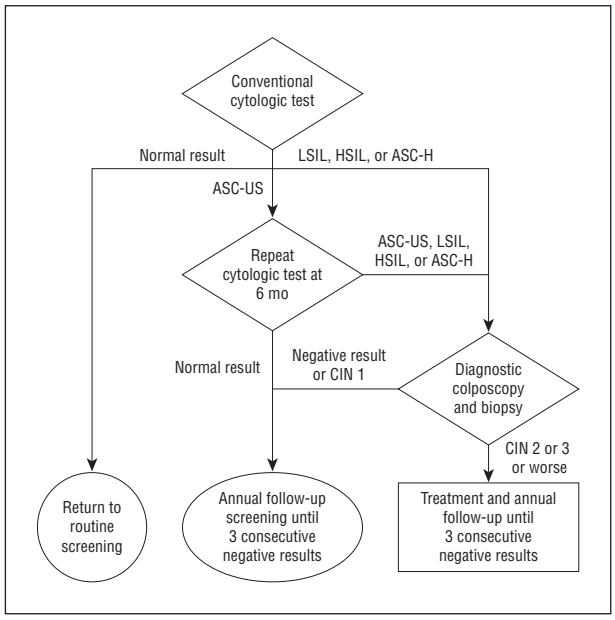

Figure 1. Screening strategy A (conventional cytologic testing followed by additional cytologic testing for atypical squamous cells of undetermined significance [ASC-US]) and the follow-up actions subsequent to all possible test results. The strategy assumes standard guidelines for follow-up and management of abnormal results.[16,17] ASC-H indicates atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesions (HSIL); CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesions.

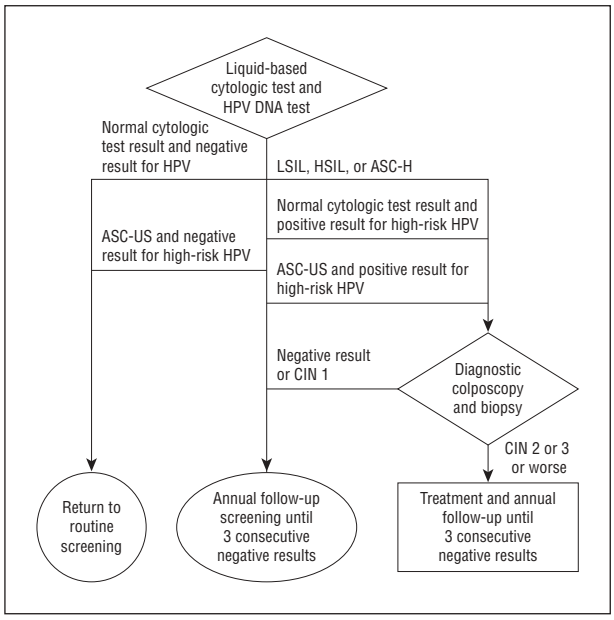

Figure 3. Screening strategy C (liquid-based cytologic testing and human papillomavirus [HPV] DNA testing in combination) and the follow-up actions subsequent to all possible test results. The strategy assumes standard guidelines for follow-up and management of abnormal results.[16,17] Other abbreviations are explained in the legend to Figure 1.

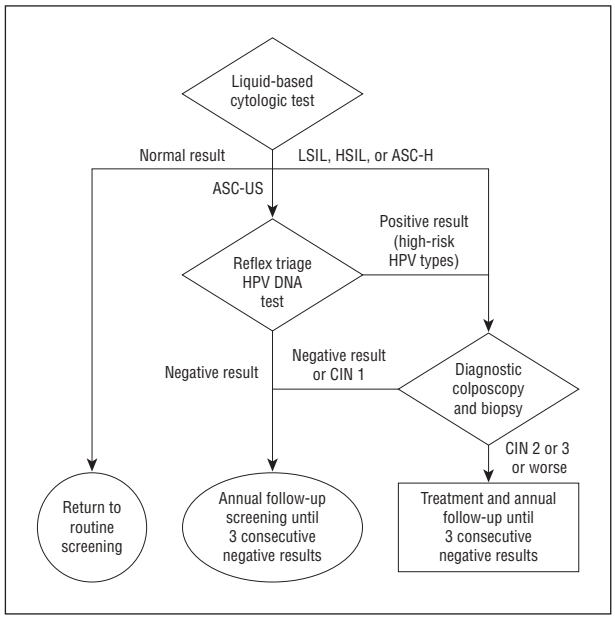

Figure 2. Screening strategy B (liquid-based cytologic testing followed by human papillomavirus [HPV] triage testing for ASC-US) and the follow-up actions subsequent to all possible test results. The strategy assumes standard guidelines for follow-up and management of abnormal results.[16,17] Other abbreviations are explained in the legend to Figure 1.

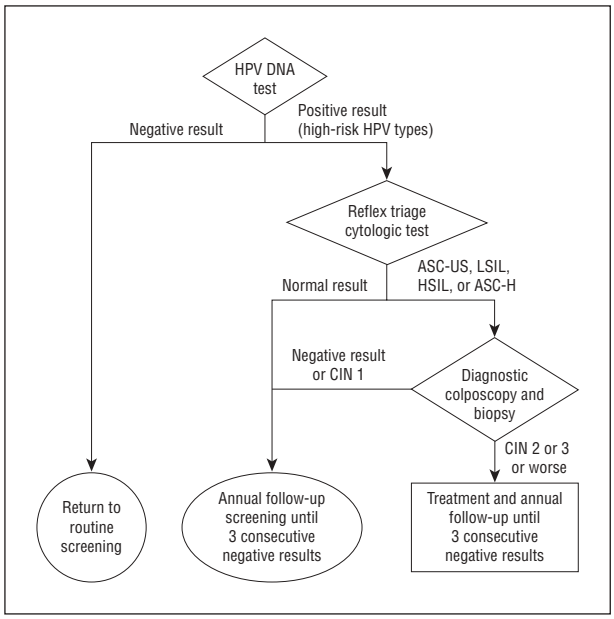

Figure 4. Screening strategy D (human papillomavirus [HPV] DNA testing followed by cytologic triage testing) and the follow-up actions subsequent to all possible test results. The strategy assumes standard guidelines for follow-up and management of abnormal results.[16,17] Other abbreviations are explained in the legend to Figure 1.

not directly benefit from vaccination but have the opportunity to benefit from new technology and improved screening strategies.

For clinical decision making, these women and their primary care physicians have a number of relevant considerations when choosing a screening strategy. Although protection from cervical cancer is the primary goal, as this risk becomes smaller, other attributes may become more important, such as potential anxiety associated with positive test results and diagnostic workup protocols.[11] Consideration of these attributes becomes even more compelling given that many diagnostic workups are in response to mild cervical abnormalities likely to regress without intervention or false-positive results. Fur-

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thermore, HPV positivity may affect a woman's quality of life because she may feel stigmatized owing to the diagnosis of a sexually transmitted infection.[12,13]

Although numerous cost-effectiveness analyses have been conducted comparing different screening approaches,[14] less attention has been paid to enumerating the more difficult to monetize trade-offs faced by individual women undergoing screening. To inform clinical decision making in the context of current and emerging screening guidelines, we assessed health-related benefits and potential harms across a spectrum of cervical cancer screening strategies using cytologic testing and HPV DNA testing. We specifically considered strategies that have been either recommended or deemed acceptable options in current US guidelines, have been used in clinical practice, or are under evaluation in clinical studies.

METHODS

ANALYTIC OVERVIEW

We used an empirically calibrated microsimulation model of the natural history of cervical cancer to simulate alternative cervical cancer screening strategies in a representative cohort of US women.[15] Strategies differed by primary screening test, triage test for abnormal results, and screening frequency. One million women were simulated individually, with a tally maintained of clinical outcomes across their lifetimes. Outcomes included number of referrals for colposcopy and detection rates of CIN 2 or 3 and cancer reported as age-specific expected outcomes from a 10-year period of screening. For descriptive purposes, we refer to colposcopies performed on women with no cervical abnormalities or with CIN 1 as "excessive." Long-term outcomes included lifetime cancer risk, life expectancy, and quality-adjusted life expectancy (QALE).

MODEL

The model, described elsewhere,[15] represents the natural history of disease as a sequence of monthly transitions between mutually exclusive health states, which include HPV infection, grade of CIN (1 and 2 or 3), and stage of cancer. The model distinguishes among HPV type 16, HPV type 18, other high-risk types, and low-risk types. The time horizon incorporates a woman's lifetime beginning at the age of 11 years before sexual debut. Transitions among health states depend on HPV type, age, history of prior HPV infection, type-specific natural immunity, previously treated CIN, and screening patterns. Women infected with HPV can develop transient CIN 1, progress to CIN 2 or 3, and regress without intervention. Women with persistent high-grade CIN may progress to invasive cancer, and those with invasive cancer can develop symptoms or progress to the next stage. Women diagnosed as having cancer receive stage-specific treatment and are subject to stage-specific survival rates. All women face competing mortality risks from all other causes.

Details of the model, calibration to epidemiologic data, and validation have been previously published.[15] Briefly, 1 million unique sets of natural history inputs were generated by sampling values from predefined ranges derived from the published literature for each model input. Simulated model outcomes produced from each set of sampled model input values were scored according to their fit with calibration targets, such as age- and type-specific HPV prevalence and age-specific cancer incidence. A subset of these sets of model inputs was selected as "good fitting" according to a likelihood-based criterion. By conducting analyses with a random sample of 25 good-fitting sets of model inputs and reporting outcomes using the mean and standard deviation, our results reflect the effect of uncertainty in model inputs.

Table 1. Flow of the Screening Strategies

Screening Strategy	Test Flow[a]	Short Name
Conventional cytologic testing with additional cytologic testing for ASC-US	A	Conventional cytologic testing
Liquid-based cytologic testing with reflex triage HPV DNA test for ASC-US	B	Cytologic testing followed by HPV triage testing
Liquid-based cytologic testing and HPV DNA test in combination	C	Combination cytologic and HPV testing
HPV DNA test with reflex triage cytologic testing for positive HPV test results	D	HPV testing followed by cytologic triage testing
Liquid-based cytologic testing with reflex triage HPV DNA test for ASC-US before age 30 y and liquid-based cytologic testing and HPV DNA test in combination at age 30 y and older	B for women aged <30 y, C for women aged ≥30 y	Cytologic testing followed by HPV triage testing, switching to combination
Liquid-based cytologic testing with reflex triage HPV DNA test for ASC-US before age 30 y and HPV DNA test with reflex triage cytology for positive HPV DNA test results at age 30 y and older	B for women aged <30 y, D for women aged ≥30 y	Cytologic testing followed by HPV triage testing, switching to HPV testing followed by cytologic triage testing

Abbreviations: ASC-H, atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesions [HSIL]; ASC-US, atypical squamous cells of unknown significance; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesions.

[a] Test flows A through D are illustrated in Figures 1 through 4, respectively.

STRATEGIES

We sought to provide comparative information on the risks and benefits of strategies recommended or deemed acceptable in US guidelines, used in clinical practice, or under evaluation in clinical studies. On the basis of these considerations, we include 4 general testing approaches that highlight important differences in the use of new technologies: conventional cytologic testing with additional cytologic testing for women with atypical squamous cells of undetermined significance (conventional cytologic testing), liquid-based cytologic testing with HPV DNA testing for women with atypical squamous cells of undetermined significance (cytologic testing followed by HPV triage testing), liquid-based cytologic testing and HPV DNA testing in combination (combined cytologic and HPV testing), and HPV DNA testing with cytologic testing for women who test positive for HPV (HPV testing followed by cytologic triage testing) (**Figures 1**, **2**, **3**, and **4** and **Table 1**). We assume

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Table 2. Expected Outcomes per 1000 Women Screened for a 10-Year Period[a]

Outcomes	Strategy A by Test Frequency, y			Strategy B by Test Frequency, y		
	1	3	5	1	3	5
Included in current US guidelines	✓	✓		✓	✓	
No. of colposcopy referrals per 1000 women screened for 10 y by age[c]						
20 y	333 (35)	157 (24)	89 (16)	403 (30)	187 (18)	107 (13)
40 y	267 (22)	127 (16)	70 (10)	300 (22)	141 (12)	77 (7)
No. of colposcopy results per 1000 women screened for 10 y by diagnosis and age[c]						
CIN 2 or 3 diagnoses						
20 y	7 (1)	7 (1)	5 (1)	7 (1)	7 (1)	5 (1)
40 y	8 (1)	8 (1)	6 (1)	9 (1)	8 (1)	6 (1)
Excessive referrals by age[c,d]						
20 y	326 (34)	150 (23)	84 (15)	396 (30)	180 (18)	102 (12)
40 y	258 (21)	118 (15)	63 (10)	291 (22)	131 (12)	70 (7)
CIN 1 diagnoses among excessive referrals by age[c,d]						
20 y	161 (35)	80 (23)	47 (15)	186 (32)	91 (19)	54 (13)
40 y	92 (22)	49 (15)	27 (10)	105 (21)	54 (12)	30 (7)
Lifetime risk of cervical cancer, %[c]	0.37 (0.08)	0.76 (0.16)	1.02 (0.19)	0.33 (0.08)	0.69 (0.14)	0.95 (0.18)
Life expectancy, y[c]	80.508 (0.008)	80.455 (0.017)	80.412 (0.024)	80.514 (0.007)	80.466 (0.016)	80.424 (0.022)

(continued)

the average age of screening initiation is 18 years, screening intervals vary from 1 to 5 years, and testing approaches may vary depending on age. For example, a representative age-based strategy is cytologic testing followed by HPV triage testing for younger women and then switching to combined cytologic and HPV testing for women older than 30 years. For comparative purposes, we simulate a status quo scenario, assuming a distribution of screening frequencies in accordance with observational data.[18]

Screening test characteristics and plausible ranges used for sensitivity analyses were based on published literature.[19,20] For both conventional and liquid-based cytologic testing, we assumed a sensitivity of 70% for CIN 1 (range, 40%-75%) and 80% for CIN 2 or 3 or worse (range, 50%-85%). We assumed a specificity of 95% (range, 90%-98%). On the basis of recent data, we also assumed a higher likelihood of a false-positive result with liquid-based cytologic testing compared with conventional cytologic testing and in particular among women with results indicating atypical squamous cells of undetermined significance.[21,22] The probability of detecting high-risk HPV types given that they are truly present and detectable is assumed to be 100%. The clinically relevant definition of the sensitivity of an HPV DNA test is the probability of detecting high-risk types of HPV given CIN 2 or 3. This is a model output and ranges from 80% to 90%, whereas specificity ranges from 87% to 92%. We conservatively assumed that diagnostic workup in response to abnormal screening test results identifies all high-grade disease and that, although it begins with colposcopy and biopsy, it may include additional procedures and subsequent screening and follow-up. We conducted a sensitivity analysis on our screening test characteristic assumptions.

We used age-specific utility weights derived from population-based data to reflect general quality of life in US females with adjustment for invasive cervical cancer.[15] To explore the potential effect on a woman's quality of life (eg, anxiety and psychosocial effects) associated with an abnormal cytologic test result, a positive HPV test result, or a diagnostic workup, we allowed for small short-term negative consequences.[11] Because the magnitude of these potential effects is uncertain, we varied them in sensitivity analyses.

RESULTS

SCREENING OUTCOMES

Table 2 gives the outcomes by screening frequency for the 4 general testing approaches using conventional cytologic testing, cytologic testing followed by HPV triage testing, combined cytologic and HPV testing, and HPV testing followed by cytologic triage testing. Table 2 also gives the outcomes for women undergoing triennial screening with cytologic testing followed by HPV triage testing before the age of 30 years who switch to HPV testing followed by cytologic triage testing at the age of 30 years to illustrate a strategy that changes the screening approach on the basis of age. Outcomes are reported as the age-specific average for a screening strategy for 1000 women participating in a 10-year period of screening. For illustrative purposes, we chose to present outcomes for 20- and 40-year-old women. Model results for all screening scenarios and ages are available from the authors by request.

REFERRAL TO COLPOSCOPY

Across strategies, referrals to colposcopy and further diagnostic workups a woman may expect from 10 years of screening varied 3-fold, although diagnostic rates of CIN 2 or 3 were similar. Screening with combined cytologic and HPV testing led to the most referrals, whereas HPV testing followed by cytologic triage testing led to the fewest. For example, for a representative group of a thousand 20-year-old women undergoing annual screening for 10 years, we expect 1795 referrals from combined cytologic and HPV testing (1788 excessive), 403 referrals from cytologic testing with HPV triage testing (396 ex-

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Table 2. Expected Outcomes per 1000 Women Screened for a 10-Year Period[a] (cont)

Outcomes	Strategy C by Test Frequency, y			Strategy D by Test Frequency, y			Age-Based Strategy by Test Frequency, y[b]
	1	3	5	1	3	5	
Included in current US guidelines		✓					
No. of colposcopy referrals per 1000 women screened for 10 y by age[c]							
20 y	1795 (286)	1038 (207)	730 (162}	223 (36)	147 (27)	107 (22)	168 (17)
40 y	901 (198)	489 (115)	291 (74)	118 (28)	77 (17)	50 (12)	77 (17)
No. of colposcopy results per 1000 women screened for 10 y by diagnosis and age[c]							
CIN 2 or 3 diagnoses							
20 y	7 (1)	7 (1)	6 (1)	6 (1)	6 (1)	5 (1)	7 (1)
40 y	9 (1)	9 (1)	7 (1)	7 (1)	7 (1)	6 (1)	7 (1)
Excessive referrals by age[c,d]							
20 y	1788 (286)	1031 (207)	724 (163)	216 (36)	141 (28)	102 (22)	161 (17)
40 y	892 (198)	480 (116)	283 (74)	110 (28)	69 (18)	43 (12)	69 (18)
CIN 1 diagnoses among excessive referrals by age[c,d]							
20 y	249 (44)	168 (33)	123 (27)	147 (32)	102 (25)	75 (19)	88 (18)
40 y	139 (30)	91 (20)	58 (14)	80 (23)	54 (15)	34 (10)	54 (15)
Lifetime risk of cervical cancer, %[c]	0.23 (0.05)	0.39 (0.09)	0.61 (0.13)	0.33 (0.08)	0.48 (0.11)	0.69 (0.15)	0.49 (0.11)
Life expectancy, y[c]	80.524 (0.004)	80.507 (0.008)	80.479 (0.013)	80.513 (0.007)	80.497 (0.010)	80.468 (0.015)	80.494 (0.010)

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

[a] The primary and triage tests for the strategies were as follows: conventional cytologic test and cytologic triage test for strategy A, cytologic test and HPV triage test for strategy B, combination cytologic and HPV test for strategy C, and HPV test followed by cytologic triage test for strategy D. For the representative age-based strategy, patients younger than 30 years had strategy B and switched to strategy D at age 30 years.

[b] This scenario switches screening strategy by the age of the woman. Women younger than 30 years are screened using cytologic testing as the primary test with HPV DNA as the triage test. Women older than 30 years are screened using HPV DNA as the primary test with cytologic testing as triage for positive HPV test results.

[c] Results are averaged across 25 sets of model inputs, have been rounded, and are given as mean (SD).

[d] Colposcopies are deemed "excessive" if the result is no lesion or CIN 1.

cessive), 333 from conventional cytologic testing (326 excessive), and 223 referrals from HPV testing followed by cytologic triage testing (216 excessive).

Less frequent screening results in lower overall referral rates but comparable trends across strategies. For the same group of 1000 women undergoing triennial screening for 10 years, we expect 1038 referrals from combined cytologic and HPV testing (1031 excessive), whereas the 3 other strategies have fewer than 200. Although the strategy of HPV testing followed by cytologic triage testing has the lowest colposcopy referrals, there is a greater likelihood of an initially positive screening test result. This finding reflects the high likelihood of HPV infection in young women because the probability of a positive test result is a function of both test sensitivity and underlying disease prevalence.

DIAGNOSIS OF CIN 2 OR 3

Although the likelihood of a CIN 2 or 3 diagnosis increases with age, most women do not have CIN 2 or 3 at the time of screening, and little variation was seen in expected diagnoses across strategies. Increasing the screening frequency from every 5 years to annually resulted in an increase of 1 to 2 more expected diagnoses of CIN 2 or 3 for a representative group of 1000 women aged 20 years undergoing 10 years of screening. For older women, the effect of screening frequency was only slightly greater.

FALSE-POSITIVE TEST RESULTS AND EXCESSIVE COLPOSCOPY USE

More than 95% of referrals to colposcopy for diagnostic workup are false positive and/or potentially excessive in that they are performed on healthy women or women who have CIN 1. Screening with combined cytologic and HPV testing, regardless of patient age, leads to the highest number of excessive colposcopic referrals. For a representative group of 1000 women aged 40 years undergoing 10 years of combination screening, we expect 892, 480, and 283 excessive referrals for colposcopy and diagnostic workup from every 1-, 3-, and 5-year screening, respectively. Of these, only 139, 91, and 58, respectively, would be for CIN 1 and the remainder conducted for women with no histologic abnormalities. Excessive referrals were reduced notably in the strategies that used triage testing.

SENSITIVITY ANALYSIS

Reductions in screening test sensitivity, whether cytologic testing or HPV DNA testing, have minimal effect on relative outcomes for strategies with frequent screening. In contrast, changes in test specificity lead to large changes in referral rates. For example, a 40-year-old woman can expect a nearly 50% increase in colposcopy referral rates if the specificity of HPV DNA testing is 10% lower than assumed in our main analysis.

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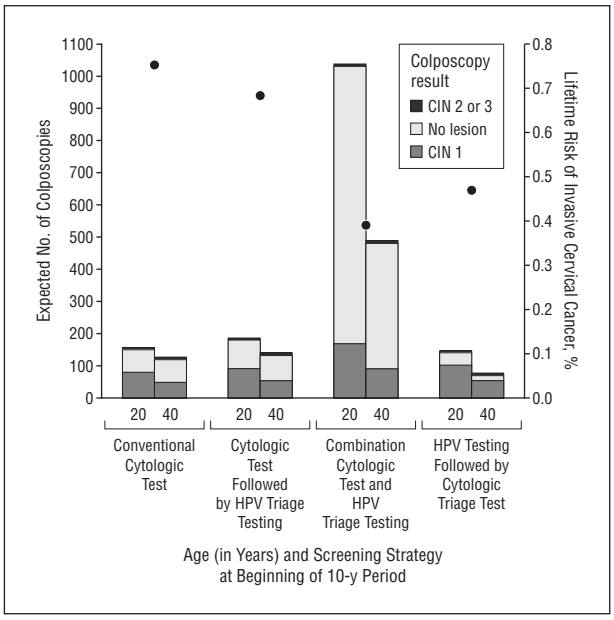

Figure 5. Expected screening outcomes and lifetime risk. Expected number of colposcopies and diagnoses of cervical intraepithelial neoplasia (CIN) types 1 and 2 or 3 among 1000 patients who undergo triennial screening for 10 years compared with the lifetime risk of invasive cervical cancer. On the left axis, the height of the bar shows the total number of colposcopies; the shaded portion is the number resulting in a diagnosis of CIN 1. The expected diagnoses of CIN 2 or 3, the solid black portion at the top of each bar, represent a small proportion of all colposcopic results (range, 6-7 for 20-year-old and 7-8 for 40-year-old women under all strategies). On the right axis, circles denote the lifetime risk of cervical cancer associated with each screening strategy. For comparison, current US screening patterns[18] resulted in a lifetime risk of cervical cancer ranging from 0.47% to 0.69%. These results represent the population perspective but may be less useful for an individual woman because the outcomes are for a population of women participating in screening at different frequencies. HPV indicates human papillomavirus.

ILLUSTRATING A BENEFIT-RISK TRADE-OFF

Figure 5 illustrates the trade-off between a measure of *benefit* (lifetime cancer risk) and *risk* (referral to colposcopy for 10 years of triennial screening) for the 4 main approaches. Differences in lifetime risk of cervical cancer among the strategies are small and translate to even smaller life expectancy differences because survival is high for cervical cancer detected at early stages as is the case for most screen-detected cancer.[1] In contrast, the colposcopy referral rate was 5-fold higher for combination cytologic and HPV testing compared with HPV testing followed by cytologic triage testing.

QUALITY OF LIFE

Table 3 gives the reductions in QALE from small disutilities associated with screening and diagnostic workup. These reductions are on the order of days and months, similar in magnitude to differences in QALE across screening frequencies and among strategies for other preventive services.[23] Considering the potential disutility from a positive screening test result, the reduction in QALE with primary HPV testing is greater than with primary cytologic test–based strategies; in contrast, the potential disutility from colposcopy has a greater effect on cytologic test–based strategies, reflecting the lower likelihood for colposcopy using primary HPV testing with cytologic triage testing. In comparing all screening frequencies and ages, the combination of cytologic and HPV testing is the least attractive because the disutility outweighs the small incremental reduction in lifetime risk of cancer.

COMMENT

To aid decision making by women and their primary care physicians, we enumerated health-related benefits and potential harms for 4 main screening strategies using cytologic and HPV DNA testing. These strategies pose trade-offs between minimizing cancer risk (already small with regular screening) and minimizing the risk of false-positive test results and excessive diagnostic procedures. Because women vary in the relative values they place on these trade-offs, providing comparative information for women and their physicians may help them choose among several screening strategies. Although no strategy will eliminate false-positive results and excessive colposcopy referrals, the risk is greater for some strategies than for others.

Although differences in a woman's lifetime cancer risk associated with alternative screening approaches are small, the difference in colposcopy referrals is 3-fold. Combined screening with 2 tests, cytologic testing and HPV DNA testing, leads to the highest number of false-positive results and excessive referrals across all screening frequencies, even when restricted to women older than 30 years. Although the sensitivity of combined cytologic and HPV testing is highest, expected CIN 2 or 3 diagnoses are similar for all 4 strategies. Combined cytologic and HPV testing also resulted in high numbers of CIN 1 diagnoses. For younger women, nearly half of all colposcopies resulted in a CIN 1 diagnosis regardless of strategy. Because most CIN 1 is likely to regress, this potential overdiagnosis may also be of particular concern, especially if conservative management guidelines are not followed and overtreatment occurs and/or if a woman's quality of life is compromised by the need for repeated visits and more frequent follow-up screening.

For women who experience short-term anxiety around screening and diagnostic workup, quality of life could be an important criterion for decision making if several screening options associated with similar cancer risk reduction are available. Although HPV testing followed by cytologic triage testing is less likely to result in a colposcopy referral than cytologic testing followed by HPV triage testing, there is a greater likelihood of an initially positive screening test result, especially in younger women, reflecting the significant prevalence of high-risk HPV infection in the second and third decades of life. Using cytologic test–based strategies in younger women minimizes the rate of both excessive diagnostic workups and HPV positive results on the initial screening test. This finding may be particularly important for women who experience additional disutility from the diagnosis of a sexually transmitted disease compared with an abnormal cytologic test result.

We purposefully focused on clinical outcomes and did not consider costs in this analysis. Cost-effectiveness

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Table 3. Effects of Short-term Disutility From Screening and Colposcopy on QALE[a]

	Strategy A by Test Frequency, y			Strategy B by Test Frequency, y			Strategy C by Test Frequency, y			Strategy D by Test Frequency, y		
	1	3	5	1	3	5	1	3	5	1	3	5
Included in current US guidelines	✓	✓		✓	✓			✓				
QALE, y[b]	70.166 (0.010)	70.108 (0.020)	70.063 (0.027)	70.173 (0.009)	70.120 (0.018)	70.075 (0.025)	70.185 (0.006)	70.165 (0.010)	70.133 (0.016)	70.173 (0.009)	70.153 (0.012)	70.121 (0.018)
Loss associated with 3-mo disutility from participation in a screening test, d[c]												
Disutility equivalent to life at 99.6%[d]	16.6	6.0	3.7	16.7	6.1	3.8	31.8	13.5	9.1	17.0	7.1	4.8
Loss associated with 3-mo disutility from a positive screening test result, d[e]												
Disutility equivalent to life at 99.6%[d]	0.9	0.4	0.2	1.1	0.4	0.3	2.3	1.2	0.8	1.5	0.8	0.6
Disutility equivalent to life at 92%[f]	22.5	8.9	5.7	27.7	10.8	7.0	58.6	29.9	21.1	38.7	21.2	15.1
Loss associated with 3-mo disutility from a colposcopy, d[g]												
Disutility equivalent to life at 98%[h]	2.1	0.9	0.6	2.4	1.0	0.7	8.1	4.3	3.0	1.0	0.6	0.5
Disutility equivalent to life at 92%[f]	10.7	4.3	2.8	12.2	5.0	3.3	40.7	21.3	15.2	5.1	3.2	2.4
Disutility equivalent to life at 83%[i]	21.3	8.7	5.6	24.4	10.0	6.5	81.4	42.6	30.3	10.2	6.5	4.7

Abbreviation: QALE, quality-adjusted life expectancy.

[a] The primary and triage tests for the strategies were as follows: conventional cytologic test and cytologic triage test for strategy A, cytologic test and HPV triage test for strategy B, cytologic HPV test only for strategy C, and HPV test and cytologic triage test for strategy D. For the representative age-based strategy, patients younger than 30 years had strategy B and switched to strategy D at age 30 years.

[b] QALE is computed as the average quality-adjusted life-years for the simulated cohort of 1 000 000 women. Baseline assumes no disutility from screening or follow-up testing and only includes age-specific reductions in quality of life. Life expectancy, as reported in Table 2, unadjusted for quality of life, is an upper bound on QALE. QALE results are averaged across 25 sets of model inputs, have been rounded, and are given as mean (SD).

[c] Quality of life is reduced for 3 months surrounding a screening test.

[d] The 3-month reduction in age-specific quality of life is equivalent to a quality weight of 0 for one-third of a day.

[e] Quality of life is reduced for 3 months after a positive screening test result.

[f] The 3-month reduction in age-specific quality of life is equivalent to a quality weight of 0 for 1 week.

[g] Quality of life is reduced for 3 months after a colposcopy.

[h] The 3-month reduction in age-specific quality of life is equivalent to a quality weight of 0 for 1.5 days.

[i] The 3-month reduction in age-specific quality of life is equivalent to a quality weight of 0 for 2 weeks.

analyses, which include the strategies examined herein, have been conducted with the goal of ascertaining comparative "value for resources" at a population level.[14] Our objective is different. Women are generally faced with multiple options deemed acceptable in clinical guidelines and may in fact make choices that differ from those strategies found to be most cost-effective.[24] We sought to provide comparative information on a broader range of attributes to allow women and their primary care physicians to select a screening approach reflective of individual preferences (**Table 4**). To make our results most useful in a real-world context, which includes decision makers who consider cost-effectiveness an important criterion or those developing prevention guidelines, we selected strategies that reflect current US practice and recommendations, have been found to be cost-effective, and/or are being evaluated in clinical studies.

Despite our focus on the individual, this analysis has implications at the population level. It has been estimated that 65 million cytologic screening tests are performed in the United States annually.[27] Considering the United States as a whole, our analysis shows that, if all women 18 to 70 years old were screened triennially using cytologic testing followed by HPV triage testing per current guidelines, more than 1 million excessive colposcopies would be performed annually. For a strategy of HPV testing followed by cytologic triage testing, 0.7 million excessive colposcopies would be expected; in sharp contrast, with a strategy of combined cytologic and HPV testing, this figure increased to 4 million. Nearly 1.5 million of these excessive diagnostic procedures could be eliminated by substituting a cytologic test–based strategy for women younger than 30 years, emphasizing why the combination strategy is not part of the recommended screening guidelines for this age group. Even for women older than 30 years, combined use of cytologic and HPV testing is associated with nearly 3 times more excessive colposcopies compared with cytologic test–based strategies and more than 5 times more than HPV followed by cytologic triage testing. Because the impli-

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Table 4. Comparison of Strategies

Strategy	Inclusion in Guidelines	Cost-effectiveness	Relative Potential for Excessive HPV Diagnosis	Relative Potential for Excessive Colposcopy Use
Conventional cytologic testing	Annually or biennially for women aged <30 y; biennially or triennially for women aged ≥30 y[a]	Yes, depending on frequency and follow-up[b]	None	Moderate
Cytologic testing followed by HPV triage testing	Annually or biennially for women aged <30 y; biennially or triennially for women aged ≥30 y[c]	Yes, depending on frequency and follow-up	Low	Moderate
Cytologic and HPV testing in combination	Triennially for women aged ≥30 y[d]	Not cost-effective[e]	High	High
HPV testing followed by cytologic triage testing	Not yet evaluated (clinical trials ongoing)[f]	Yes, for women aged ≥30 y[g]	High	Low

Abbreviation: HPV, human papillomavirus.
[a] Recommended by the American College of Obstetricians-Gynecologists, US Preventive Services Task Force, American Cancer Society.[2-5]
[b] See Goldie et al.[14]
[c] Recommended by the Interim Consensus Group.[3]
[d] Suggested as a reasonable alternative to cytology-based screening options by American College of Obstetricians-Gynecologists, American Cancer Society, and the Interim Consensus Group.[2-4]
[e] Combination screening has been reported to have very high incremental cost-effectiveness ratios when compared with other screening strategies.[14]
[f] Clinical trials are ongoing.[6]
[g] See Goldhaber-Fiebert et al[25] and Sherlaw-Johnson and Phillips.[26]

cations for resource utilization could be substantial, this information might be useful to other decision makers, such as health care organizations responsible for providing care to their insured populations.

For our analysis we used a modeling approach and, as such, formidable limitations are related to the data and assumptions necessary for the model. The natural history of HPV infection and cervical cancer is unobservable. As with any model, unobservable variables were constrained by structural assumptions and fit to epidemiologic data. Our model is biologically plausible and produces results consistent with observational data.[15] To establish an upper bound on both the risks and benefits achievable, we assumed 100% adherence to the screening protocol for each strategy. One can infer by the results for other screening frequencies what outcomes would be if women participated less regularly. Finally, we did not address qualitative aspects that affect women's decision making regarding screening participation (eg, preferences for screening frequency, presentation of numerical results, or peace of mind from diagnostic resolution).

The newly available HPV 16 and 18 vaccine will pose additional challenges to the evaluation of screening policies. If long-term performance of the HPV vaccines is as promising as the short-term performance,[7,8] the marginal health benefit from screening will be even smaller, potentially accentuating trade-offs in risks among strategies for some women. Although the effect of widespread use of the vaccine on HPV infection dynamics is as yet unknown and will not be known for several years, the relative performance of cytologic and HPV DNA testing will likely be affected.[28] Undoubtedly, in vaccinated women, the ratio of false-positive to true-positive screening test results will increase if screening strategies remain the same. Although we chose to focus on providing information to women making decisions about screening today, these issues will be critical to explore in terms of both empirical data analysis and cost-effectiveness analysis.

There is great promise in the availability of accurate HPV diagnostics, new screening technology, and HPV vaccination for successful cervical cancer prevention in the United States. From both an individual and population perspective, the range of new options for prevention will ideally be assembled in such a way as to improve cancer outcomes, reduce disparities, and minimize the risk of overdetection of abnormalities likely to resolve on their own. As the risk of cervical cancer becomes small, in part owing to an already successful secondary prevention program and the availability of new technologies, women and their primary care physicians may wish to consider their choices in the context of a more fully descriptive range of screening strategy attributes. Existing information, however, about cervical cancer prevention directed toward the lay public has not always presented the benefits and risks from screening in a manner that illustrates all potential consequences.[29] We sought to provide insight into the trade-offs associated with a range of cervical cancer screening policies. These results provide an initial step toward a comprehensive set of clinically relevant information highlighting trade-offs among screening policies to ultimately better inform women's decisions and provide additional dimensions for the construction of clinical guidelines.

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