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Screening for Cervical Cancer: A Modeling Study for the U.S. Preventive Services Task Force

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Abstract

Objective—This study addresses three questions posed by the United States Preventive Services Task Force (USPSTF): 1) At what age should screening for cervical cancer begin; 2) At what age should screening for cervical cancer end; and 3) How do the benefits and potential harms of screening strategies that use human papillomavirus (HPV) DNA testing in conjunction with cytology (co-testing) compare to those strategies that use cytology only?

Methods—A Markov model was updated and used to quantify clinical outcomes (i.e. colposcopies, cancers, life expectancy) associated with different screening strategies.

Results—Screening in the teenage years is associated with a high number of colposcopies small differences in cancers detected and, as a result, small gains in life expectancy. Screening women beginning in the early 20s provides a reasonable balance of the harms and benefits of screening. Among women who have been screened according to the current recommendations for cervical cancer (beginning at age 21, and conducted every 3 years with cytology), screening beyond age 65 is associated with small additional gains in life expectancy but large increases in colposcopies. In terms of co-testing, a strategy of cytology only conducted every 3 years, followed by co-testing conducted every 5 years (for women aged 30+ years) is associated with fewer colposcopies and greater gains in life-expectancy compared to screening with cytology-only conducted every 3 years.

Conclusions—The results of this modeling study support current USPSTF recommendations for cervical cancer screening.

Keywords

cervical cancer screening; colposcopies; modeling

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Conflicts of Interest

For the remaining authors no conflicts of interest are declared.

INTRODUCTION

In the United States, approximately 12,710 women were diagnosed with and 4,290 women died from cervical cancer in 2011. (1) Assuming no change in risk, approximately 0.68% of women born today in the U.S. will be diagnosed with cervical cancer at some time during their lifetime; the risk of dying from the disease is 0.24%. The low incidence of and mortality from cervical cancer is attributable to cytology-based screening and the treatment of cervical intraepithelial neoplasia (CIN). (2) The U.S. Preventive Services Task Force (USPSTF) currently recommends that women begin cytology-based screening for cervical cancer within 3 years of onset of sexual activity or by age 21 (whichever comes first). (3) The Task Force recommends against routinely screening women aged 65 years or older if they have had an adequate recent screening with normal cytologic smears.

Human papillomavirus (HPV) DNA testing has been studied as an alternative or complementary approach to cytology screening. Ongoing and completed screening studies comparing these tests suggest that under certain circumstances, the use of HPV DNA tests may provide further reductions in cervical cancer incidence but with a potential increase in screening burden. (4) In 2010, the Task Force requested a systematic review of the evidence as well as a modeling study to inform any revisions to the previous (2003) recommendations for cervical cancer screening. The new recommendations were published in March, 2012. (3) This manuscript summarizes the results of the modeling study that was used to inform these most recent recommendations.

The goals of the study were to use simulation modeling to address three questions posed by the USPSTF: 1) What is the appropriate age at which to begin screening for cervical cancer? 2) What is the appropriate age at which to end screening for cervical cancer; and 3) How do screening strategies that use HPV DNA testing in conjunction with cytology compare with screening strategies that use cytology only in terms of benefits (quantified using life-years) and potential harms (quantified using colposcopies).

METHODS

Markov Model

A previously described Markov model of the natural history of HPV and cervical cancer (developed using TreeAgePro 2010® (Williamstown, MA)) was updated for this study. (5) The updates included a review of the literature on the natural history of HPV (all types) and cervical intraepithelial neoplasia (CIN) using PubMed (for articles published prior to August 2010); based on this review, new estimates of progression to cancer were included in the model. In addition, estimates of survival, mortality, and hysterectomy for benign conditions were updated (details are provided in the Appendix of a published Evidence Report). (6) The model follows a theoretical cohort of unvaccinated women from age 12 to 100 years and assumes that, at the beginning of the simulation, no one is infected with HPV or has CIN or cancer. Cycle lengths are 1 year. The model assumes women in the cohort can be infected with HPV each year. It also assumes that women infected with HPV can undergo regression, no change, or progression to cervical intraepithelial neoplasia (CIN). Women in the cohort with CIN 1 can undergo regression (to either "Well" or the HPV-infected state), no change, or progression to CIN 2–3. Women with CIN 2–3 can regress, stay in the same state or progress to Stage I cancer. Women with cancer either become symptomatic or progress through Stages II–IV. Once a cancer diagnosis is made, the probability of survival is stage-specific. Women in the cohort without cancer are assumed to be at risk of having a benign hysterectomy, and all the cohort women are assumed to be at risk for death from other causes.

Screening Strategies

The model was used to estimate the number of colposcopies (the clinical burden) and life years gained (the clinical benefit) for screening strategies that differed by question. For the question of the age to begin screening, the age at which the first screening was assumed to occur was varied in 1 year increments from age 15 years to 25 years. All women in the cohort were assumed to end screening at age 85 years. For the question of the age at which to end screening, two different screening strategies were modeled based on the assumption that: 1) women had been screened every 3 years from age 21 to age 65 years, consistent with the current recommendations or, 2) women had never been screened prior to age 65 years. For the latter strategy, the first screening test was assumed to occur at age 65. The age to end screening was then varied in 5 years increments up to age 90 years.

For both questions (the age at which to begin screening and the age at which to end screening), screening was assumed to be conducted with cytology with a repeat cytology test for atypical squamous cells -- undetermined significance (ASC-US), and referral to colposcopy for those with atypical squamous cells --high grade (ASC-H), low-grade squamous intraepithelial lesions (LSIL), or a more severe result. Screening was assumed to be conducted at intervals of every 1, 2, 3, or 5 years.

For the third question, which compared cytology-only based screening strategies to strategies that combined HPV and cytology, the following was modeled: Women in the cohort aged <30 years were assumed to be screened with cytology only, with repeat cytology for ASC-US or referral to immediate colposcopy if ASC-H or LSIL. The interval for screening prior to age 30 was varied from 1 to 3 years. All women in the cohort 30 years and older were assumed to receive HPV and cytology (i.e. co-testing) with subsequent triage as follows: (1) women with LSIL cytology results or ASC-US cytology results with a positive HPV result were assumed to be referred to colposcopy; (2) women with an AS-CUS cytology who had a negative HPV test result were assumed to undergo repeat testing in 1 year; (3) women with a normal cytology test result but who had a positive HPV test were assumed to undergo repeat testing in 1 year; and (4) women with normal cytology and negative HPV tests results were assumed to return to routine screening conducted every 3 years or 5 years.

Additional assumptions were as follows:

1. Colposcopy and biopsy were assumed to be perfectly sensitive and specific for the main analyses (i.e., base case) consistent with its current use as the standard for clinical care; this assumption was examined in sensitivity analyses. (7, 8)
2. Follow-up for abnormal screening test results and abnormal histology was modeled based on recently published American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines.(7) Women aged <21 years were assumed to be treated according to the guidelines for adolescent women who have abnormal screening test results and/or histology results.
3. Adherence to screening, follow-up, and treatment was assumed to be 100% for the base case but varied in sensitivity analyses.

Screening Test Sensitivity and Specificity

Estimates of sensitivity and specificity for Hybrid Capture® 2 (hc2) high-risk HPV DNA test (Qiagen, Valencia, CA) and cytology were based on estimates from a systematic review prepared by the Oregon Evidence Practice Center (9), as well as on estimates derived from the literature.(4), (10) For the purposes of this analysis, we used the term “cytology” to refer to both liquid-based cytology and conventional cytology; this decision was based on recent

data showing no statistically significant difference between the two tests in terms of sensitivity and specificity.(10) For this study, HPV DNA testing was assumed to be conducted with hc2. Cytology results of atypical squamous cells of unknown significance (ASCUS) or more severe results were considered abnormal; a positive hc2 test result was based on an RLU/CO = 1. For the age to begin and age to end screening questions, a single set of estimates of cytology test accuracy based on studies identified in the systematic review (referred to as Oregon EPC report-based estimates) as high quality with good applicability to the United States was used for the base case; estimates from other studies identified as relevant to the United States were used to provide ranges for the sensitivity analyses.(10) For the HPV and cytology question, we used two additional sets of estimates for hc2 and cytology test accuracy to reflect marked variation in the magnitude of the difference in sensitivity and specificity between the two tests. One was derived from a large randomized controlled trial of HPV testing and cytology (Mayrand et al. 2007); the other was derived from a meta-analysis conducted by Koliopoulos et al. (2007).(4, 8) These estimates (and ranges) are presented in Table 1; results based on these estimates are referred to as Mayrand et al. and Koliopoulos et al.

Analytic Approach

Base Case Analyses—For each question, the following outcomes were calculated (per 1,000 women): expected false-positive test results, colposcopies performed, cervical intraepithelial neoplasia grade 2–3 (CIN 2–3) lesions detected, cervical cancers and cervical cancer deaths. The main outcome for this analysis was colposcopies per (undiscounted) life-year gained. A previous analysis conducted for the USPSTF on screening for colorectal cancer used colonoscopies per life-year gained as the primary outcome.(11) Colposcopy, the current standard for definitive diagnosis after an abnormal cervical cancer screening result, was chosen as the closest analogue to colonoscopy.

Strategies were compared using incremental ratios based on the difference in expected number of colposcopies, divided by the difference in life expectancy. Strategies that were associated with more colposcopies and were less effective or were associated with fewer colposcopies but had a higher colposcopy per life-year gained ratio than an adjacent strategy were considered to be dominated, a term used in health economics to refer to inefficient strategies.(12) The remaining strategies (after this elimination process) lie on an “efficiency frontier”.

Sensitivity Analyses—For each question, one-way sensitivity analyses were conducted in which the following were varied: natural history, screening adherence, sensitivity and specificity of colposcopy and biopsy, and screening and triage test sensitivity and specificity. One concern with the use of colposcopies per life-year is that this measure may underestimate the burden of screening. This is because the ASCCP guidelines (7) allow for adolescent women aged <21 years to be retested if they have an abnormal cytology test result. The ASCCP guidelines also call for repeat testing with cytology and HPV tests for women with discordant results if they initially undergo co-testing. To address this, sensitivity analyses were conducted that estimated the number of tests (performed for screening or screening and triage) per life-year for the age to begin question and for the cytology and HPV question.

For the cytology and HPV question, a sensitivity analysis was conducted that included a strategy of HPV DNA testing with cytology triage for women with positive HPV results (i.e. sequential testing). It should be noted that this strategy is not currently recommended for cervical cancer screening. For this strategy, women aged <30 years were assumed to be screened with cytology only, with repeat cytology for ASC-US or referral to immediate

colposcopy if ASC-H or LSIL. All women 30 years and older were assumed to have an HPV test done initially. Women who were HPV positive were assumed to receive cytology testing. If their cytology test result was AS-CUS, they were assumed to undergo colposcopy; if their cytology test result was normal, they were assumed to undergo repeat testing in 1 year with referral to colposcopy if they had a subsequent abnormality. Women with negative HPV results were assumed to return to routine HPV-based screening conducted every 1, 2, 3, or 5 years.

RESULTS

Age to Begin Screening

An increasing age of first screening is generally associated with fewer false-positive test results, fewer colposcopies, and fewer CIN 2–3s, but an increase in cancers and cancer deaths (Table 2; estimates presented are for ages 15, 18, 21 and 25). The largest number of false-positive test results (over a lifetime) occurs in adolescents aged <21 years (range per 1,000 women: 960 at age 20 years to 1,003 at age 15 years for annual screening). This age group also has the lowest number of expected cancer cases (range per 1,000 women, <3). Although the number of false-positive test results is smaller (ranged from 872 per 1,000 at age 25 years to 932 at age 22 years) with each successive year that screening is delayed beyond age 21 years (compared with beginning at age 21 years) the number of expected cancer cases rises (2.5 to 2.86 per 1000 women). Of note, approximately 70% of CIN 2–3 are estimated to be CIN 2's in women aged <25 years. In terms of screening interval, screening every 5 years beginning at age 21 is associated with a difference in cancer mortality of 2.4 per 1000 women and a difference in cancer incidence of approximately 10.2 per 1000 women compared with screening every year. Screening every year is associated with an almost 4-fold increase in the number of colposcopies performed compared with screening every 5 years.

Taken together, these patterns explain the base case findings presented in Figure 1. If the strategies that fall on the steepest part of the efficiency curve are assumed to represent a reasonable trade-off between colposcopies and life expectancy gains, then strategies of screening every 3 to 5 years beginning in the early 20s are more attractive compared with those strategies that are based on screening every year in the early teens.

Sensitivity analyses confirm the base-case findings, namely that screening frequently in the teen-age years is associated with a large number of colposcopies, but relatively small gains in life expectancy. A sensitivity analysis that uses screening cytology tests per life-year (Table 3) also shows that screening in the teens is associated with a high number of cytology tests per life-year gained. As part of this analysis, a strategy of screening beginning at age 21 and conducted at least every 3 years (as currently recommended) is identified as efficient.

Age to End Screening

Among women who have never been screened prior to age 65 years, varying the age to discontinue screening (if screening is assumed to commence at age 65 and end at either age 70, 75, 80, 85 or 90 years) has a relatively small impact on cancer cases and cancer deaths, but a large impact on the number of colposcopies and false positive test results (Table 4). For example, cancer deaths range from approximately 9 per 1,000 women if screening is conducted every 5 years and ended at age 70 to approximately 8 per 1,000 women if screening ends at age 90. For the same comparison, colposcopies range from approximately 37 to 136 per 1,000 women. A similar pattern is seen when frequency of screening is increased – small reductions in cancer cases and deaths, but large increases in false-positives and colposcopies. As a result, among women who have never been screened prior to age 65

years, strategies associated with infrequent screening (every 2 through 5 years) beginning at age 65 and ending at age 70 years fall on the steep part of the curve and are considered efficient (Figure 2-1).

In contrast, women who have been screened every 3 years beginning at age 21, as currently recommended, derive marginal benefit from screening beyond age 65 years (Table 5). As a result, the strategies depicted in Figure 2-2 cluster together based on life expectancy, with an approximately 1-year gain in life expectancy per 1,000 women at most, which represents less than a day's gain in life expectancy per woman. These results are robust across a range of sensitivity analyses including analyses which assume less than perfect compliance with screening, and low estimates for screening test sensitivity.

Cytology Testing Alone Compared With Cytology and HPV The results for this analysis (Table 6) are similar regardless of the estimates used: there are fewer colposcopies but more cancers and cancer deaths associated with screening using cytology tests conducted at intervals of every 2, 3, and 5 years compared with screening with cytology only prior to age 30 (conducted at intervals of every 1, 2, or 3 years), and then with cytology and HPV (co-testing) beginning at age 30 (conducted every 3 or 5 years). However, when the cytology-only strategy is conducted annually, it is associated with more colposcopies but fewer cases of cancer and cancer deaths, compared with the co-testing strategies. This is due to women with dually negative results for the co-testing strategy being screened every 3 or 5 years; as a result, there are more cases of disease compared with the cytology only strategy conducted annually. Of note, a strategy of cytology only conducted every 3 years is associated with more colposcopies and cancers compared to a strategy of cytology only conducted every 3 years prior to age 30, followed by co-testing with HPV and cytology every 5 years (for women normal results).

As a result, as shown, HPV and cytology strategies are identified as providing a potentially reasonable trade-off between the burden and benefits of screening (Figure 3; results presented are based on the Oregon EPC report-based estimates) compared to cytology-only strategies. These findings are generally similar across a range of sensitivity analyses. Exceptions occur when screening and triage tests are used to reflect the burden of screening instead of colposcopies and when a strategy of HPV followed by cytology for HPV positive women (i.e. sequential testing) is modeled. The strategy of HPV followed by cytology, although not currently recommended, is identified as efficient compared with either the cytology-only or co-testing strategies (Table 7). This is because only women with positive results on both tests are initially referred to colposcopy, thus reducing the burden of colposcopies due to false positive results. Those with discordant results (HPV positive, normal cytology) are assumed to undergo repeat screening with HPV and cytology a year later, with referral to colposcopy if repeat testing is abnormal. Thus this strategy detects more cancers compared to cytology, and, as a result, is associated with a higher life-expectancy. Compared to co-testing (i.e. parallel testing with HPV and cytology), a strategy of HPV followed sequentially by cytology is associated with fewer colposcopies but lower life-expectancy when conducted at intervals of every 3 or 5 years, and higher life-expectancy when conducted at intervals of every 1 or 2 years. As a result, strategies of HPV and cytology (co-testing) are considered less efficient because they are associated with less attractive colposcopy per life year gained ratios.

DISCUSSION

The current analysis was designed to respond to specific questions posed by the USPSTF regarding the burdens and benefits of screening strategies for cervical cancer. Our analyses show that screening in the teenage years is not efficient due to the high number of

colposcopies but small gains in life expectancy afforded. A large percentage of high-grade lesions are estimated to be CIN 2, which is more likely to regress in younger women. As such, detection of CIN 2–3 in this population may result in over-diagnosis and over-treatment. This is important because studies of cone or loop electrosurgical excision procedure treatments for CIN in reproductive aged-women have shown an association with an increased risk of adverse pregnancy outcomes.(13), (14) However, if the age of first screening is delayed past age 21, there is an increasing risk of cancer for each year of delay. In terms of the age to end screening, our results support the current recommendation that women who have been screened per recommendations (every 3 years beginning at age 21) until age 65 years can discontinue screening. In this group, any further screening is associated with very small gains in life expectancy that are achieved at the expense of a large number of colposcopies.

Our results for HPV testing in conjunction with cytology show that co-testing conducted every 5 years (for women aged 30 years or older) may be associated with fewer colposcopies and greater gains in life-expectancy compared to the currently recommended strategy of screening with cytology only conducted every 3 years. However, this finding is sensitive to the metric chosen to quantify the burden of testing. Although cytology and HPV (co-testing) strategies are generally identified as efficient using colposcopies per life-year, cytology-only strategies are also identified as efficient if tests are used to quantify burden of screening. This finding highlights a limitation of this analysis, namely, that it was performed specifically to assist the USPSTF in its development of recommendations for cervical cancer screening, which may limit the generalizability of the results. Although the USPSTF chose colposcopies per life-year gained as the metric used to summarize the balance between the clinical burden and benefits of screening, it remains unclear to what extent colposcopies represent a burden to women who undergo cervical cancer screening and what threshold of colposcopies per life-year gained should be used to define “high-burden.” Another limitation is that the analyses as presented do not follow a traditional decision analysis format in which all strategies are simultaneously considered. For this study, each question was addressed separately at the request of the USPSTF. For example, for the age to begin screening question, the age to end screening was fixed so that differences between strategies could be attributed to variation in the age to begin only. However, the usual recommended approach for a traditional decision analysis would be to simultaneously vary the age to begin and age to end.

Other potential limitations include use of data for HPV DNA testing based on hc 2. Other HPV tests that have recently been approved for use in the United States include the Cervista tests (Hologic, Inc., Bedford, MA) and cobas HPV test (Roche, Pleasanton, CA); as data on the performance characteristics of these tests in population-based screening are published, additional analyses will be needed to determine which tests, if any, should be recommended for use. A final limitation of this analysis is that the USPSTF requested that we not consider the impact of HPV vaccines due to a lack of published data on the long-term benefits of vaccination, including reductions in cancer incidence and mortality. New analyses, which address these limitations, will be needed as data become available.

Conclusions

In conclusion, the results of this modeling study support the current USPSTF recommendation of beginning screening at age 21 years. The results of this study also support the current recommendation to end screening at age 65 years. This analysis suggests that a strategy of screening with cytology only conducted every 3 years prior to age 30 followed by co-testing with HPV and cytology, conducted every 5 years for women 30 years and older may be associated with fewer colposcopies and greater gains in life-expectancy compared to screening with cytology only conducted every 3 years. Finally, our analyses

suggest that a strategy that is not currently recommended, of HPV followed by cytology for HPV positive women (i.e. sequential testing) may provide a reasonable trade-off between the burden and benefits of screening and warrants further study.

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REFERENCES

1. Howlader N, NA.; Krapcho, M.; Neyman, N.; Aminou, R.; Waldron, W.; Altekruse, SF.; Kosary, CL.; Ruhl, J.; Tatalovich, Z.; Cho, H.; Mariotto, A.; Eisner, MP.; Lewis, DR.; Chen, HS.; Feuer, EJ.; Cronin, KA.; Edwards, BK., editors. SEER Cancer Statistics Review, 1975–2008. Bethesda, MD: National Cancer Institute; 2011. http://seercancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site
2. Gustafsson L, Ponten J, Zack M, Adami HO. International incidence rates of invasive cervical cancer after introduction of cytological screening. *CA Causes Control*. 1997 Sep; 8(5):755–763.
3. Moyer VA. Screening for Cervical Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2012 Mar 14.
4. Koliopoulos G, Arbyn M, Martin-Hirsch P, Kyrgiou M, Prendiville W, Paraskevaidis E. Diagnostic accuracy of human papillomavirus testing in primary cervical screening: a systematic review and meta-analysis of non-randomized studies. *Gynecol Oncol*. 2007 Jan; 104(1):232–246. [PubMed: 17084886]
5. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *Am J Epidemiol*. 2000 Jun 15; 151(12):1158–1171. [PubMed: 10905528]
6. Kulasingam, SL.; Havrilesky, L.; Ghebre, R.; Myers, ER. Screening for Cervical Cancer: A Decision Analysis for the U.S. Preventive Services Task Force. Services Task Force; 2011 May.
7. American Society for Colposcopy and Cervical Pathology (ASCCP). Consensus Guidelines2006. [cited draft report: Available from: <http://www.asccp.org/consensus.shtml>
8. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol*. 2007 Oct; 197(4):346–355. [PubMed: 17904957]
9. Vesco, K.; Whitlock, E.; Eder, M.; Lin, J.; Burda, B.; Senger, C., et al. Screening for Cervical Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No 86 AHRQ Publication No 11-05156-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2011.
10. Mayrand MH, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med*. 2007 Oct 18; 357(16):1579–1588. [PubMed: 17942871]
11. Zuber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S.

- Preventive Services Task Force. Ann Intern Med. 2008 Nov 4; 149(9):659–669. [PubMed: 18838717]
12. Gold MR, SJ.; Russell, LB.; Weinstein, MC., editors. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
 13. Arbyn M, Kyrgiou M, Simoons C, Raifu AO, Koliopoulos G, Martin-Hirsch P, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. BMJ. 2008; 337:a1284. [PubMed: 18801868]
 14. Sadler L, Saftlas A, Wang W, Exeter M, Whittaker J, McCowan L. Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. JAMA. 2004 May 5; 291(17):2100–2106. [PubMed: 15126438]

Figure 1.

Efficiency curve comparing strategies that differ by age of first screening. Strategies presented are those identified as efficient using incremental colposcopies per life-year.

*Note: the steep part of the curve is considered to include the most efficient strategies, since these provide more life expectancy gains per colposcopy than the flatter part of the curve where progressively smaller life expectancy gains occur for an increasing number of colposcopies.

Figure 2.

Efficiency curve* comparing strategies that differ based on age to end screening among women who have not been screened prior to age 65 (1) and among women who have been screened every 3 years beginning at age 21, to age 65 (2). Screening is varied by interval (q1, q2 (for those who have not been screened prior to age 65; q3 and q5) and age to end (70, 75, 80, 85, 90). Strategies presented are those identified as efficient using colposcopies per (undiscounted) life-years.

*Note: the steep part of the curve is considered to include the most efficient strategies, since these provide more life expectancy gains per colposcopy than the flatter part of the curve

where progressively smaller life expectancy gains occur for an increasing number of colposcopies.

Figure 3.

Efficiency curve comparing strategies based on cytology either alone or in combination with HPV. Strategies presented are those identified as efficient using incremental colposcopies per life year.

*Note: the steep part of the curve is considered to include the most efficient strategies, since these provide more life expectancy gains per colposcopy than the flatter part of the curve where progressively smaller life expectancy gains occur for an increasing number of colposcopies.

Table 1

Sensitivity and specificity of cytology and HPV testing for primary screening and triage of abnormal cytology results. * † 4,9–10

Screening or Triage Test	Sensitivity of test for CIN 2+	Specificity of test for <CIN 2	Delta of HPV compared to cytology in same study	
Cytology			Sensitivity (CIN2+)	Specificity (CIN2+)
Primary Screening				
Oregon EPC Report (2011) ⁹	0.569	0.945		
Mayrand et al. (2007) ¹⁰	0.564	0.973		
Koliopoulos et al. (2007) ⁴ meta-analysis	0.727	0.919		
Range	0.20–0.772	0.847–0.990		
Triage for ASC-US	0.762	0.638		
Range	0.45–0.956	0.475–0.756		
HPV DNA using hc2				
Primary Screening				
Oregon EPC Report (2011) ⁹	0.964	0.906	0.395	–0.039
Mayrand et al. (2007) ¹⁰	0.974	0.943	0.41	–0.03
Koliopoulos et al. (2007) ⁴ meta-analysis	0.948	0.86	0.221	–0.059
Range	0.341–1.00	0.767–0.966		
Triage for ASC-US	0.892	0.641	0.13	0.003
Range	0.67–0.976	0.31–0.672		

* A cytology result of ASC-US or greater is considered an abnormal result.

† A positive hc2 test result is based on a cut-point of an RLU/CO = 1.

Table 2

Expected false-positives, colposcopies, CIN 2–3s, cancer cases and cancer deaths (per 1000 women) associated with screening beginning at age 15, and increased in one-year increments up to and including age 25. *Screening intervals of every one (q1), two (q2), three (q3) and five (q5) years are compared. Women are followed for a lifetime

Strategy	Age 15	Age 18	Age 21	Age 25
q5 False Positives	220.74	217.50	213.97	201.86
q3 False Positives	367.97	358.93	349.92	323.33
q2 False Positives	542.21	520.72	515.26	472.93
q1 False Positives	1002.73	977.09	951.45	871.61
q5 Colposcopies	481.05	483.13	483.36	461.00
q3 Colposcopies	776.54	767.48	758.16	706.79
q2 Colposcopies	1,110.92	1,076.87	1,083.52	1,001.77
q1 Colposcopies	1,982.10	1,956.35	1,931.00	1,777.71
q5 CIN 2–3s	67.38	67.12	66.01	66.25
q3 CIN 2–3s	80.55	80.53	80.21	79.03
q2 CIN 2–3s	88.01	87.59	87.52	85.92
q1 CIN 2–3s	92.14	92.04	91.50	90.08
q5 Cancer Cases	12.70	12.66	12.69	12.89
q3 Cancer Cases	8.45	8.45	8.50	8.82
q2 Cancer Cases	5.73	5.73	5.80	6.14
q1 Cancer Cases	2.41	2.42	2.50	2.86
q5 Cancer Deaths	2.70	2.69	2.71	2.75
q3 Cancer Deaths	1.54	1.54	1.55	1.62
q2 Cancer Deaths	0.90	0.91	0.92	1.00
q1 Cancer Deaths	0.31	0.31	0.32	0.40

* Results for ages 15, 18, 21 and 25 are presented. Results for all ages are presented in a report.⁶

Table 3

Sensitivity analysis showing expected cytology tests, incremental cytology tests, life-years, incremental life-years, and incremental cytology tests per life-year associated with screening beginning at different ages per 1,000 women. Screening varies in 1-year increments from age 15 to 25 years. Screening intervals of 1 (q1), 2 (q2), 3 (q3), and 5 years (q5) are compared.

Strategy	Cytology Tests	Incremental Tests	Life-Years	Incremental Life-Years	Incremental Cytology Tests per Life-Year
No intervention	0		69016.30		
Age 25, q5	9834	9834	69178.79	162.49	61
Age 23, q5	10139	305	69181.25	2.46	124
Age 22, q5	10266	127	69182.04	0.79	161
Age 24, q3	15998	5732	69210.25	28.21	203
Age 22, q3	16747	749	69212.10	1.85	405
Age 21, q3	16999	252	69212.70	0.60	420
Age 24, q2	23406	6407	69227.31	14.61	439
Age 22, q2	24406	1000	69229.32	2.01	498
Age 20, q2	25402	996	69230.20	0.88	1132
Age 22, q1	45386	19984	69245.87	15.67	1275
Age 21, q1	46333	947	69246.58	0.71	1334
Age 20, q1	47277	944	69246.92	0.34	2776
Age 19, q1	48219	942	69247.21	0.29	3248
Age 18, q1	49162	943	69247.39	0.18	5239
Age 17, q1	50105	943	69247.48	0.09	10478
Age 16, q1	51049	944	69247.51	0.03	31467
Age 15, q1	51993	944	69247.51 *	<.01	219524

* Rounded estimate.

Table 4

Expected false-positives, colposcopies, CIN 2–3s, cancer cases and cancer deaths per 1000 women associated with different ages to end screening (varied in five year increments from age 65 to 90). Women are assumed to never have been screened prior to age 65. Thereafter, they are screened until age 70, 75, 80, 85 or 90. Screening intervals of every one (q1), two (q2), three (q3) and five (q5) years are compared. *, †

	Age 70	Age 75	Age 80	Age 85	Age 90
No Screening (until Age 65)					
q5 False Positives	13.72	36.82	46.08	52.60	56.07
q3 False Positives	26.24	49.63	68.71	76.60	85.78
q2 False Positives	38.65	72.77	92.51	114.36	122.99
q1 False Positives	72.43	125.82	170.98	205.32	225.27
No Screening (until Age 65)					
q5 Colposcopies	36.95	91.70	112.94	127.84	135.78
q3 Colposcopies	66.49	118.54	160.44	177.64	197.81
q2 Colposcopies	93.45	166.42	208.35	254.84	273.17
q1 Colposcopies	162.55	272.12	364.75	435.21	476.15
No Screening (until Age 65)					
q5 CIN 2–3s	8.16	16.49	19.31	21.26	22.28
q3 CIN 2–3s	12.55	18.32	22.61	24.29	26.36
q2 CIN 2–3s	15.02	20.94	24.14	27.75	29.15
q1 CIN 2–3s	18.07	23.08	27.26	30.45	32.31
No Screening (until Age 65)					
q5 Cancer Cases	28.76	27.30	27.02	26.91	26.88
q3 Cancer Cases	27.84	26.80	26.26	26.12	26.00
q2 Cancer Cases	27.29	26.20	25.76	25.43	25.34
q1 Cancer Cases	26.51	25.51	24.88	24.55	24.40
No Screening (until Age 65)					
q5 Cancer Deaths	8.60	8.04	7.95	7.91	7.89
q3 Cancer Deaths	8.24	7.88	7.71	7.67	7.64
q2 Cancer Deaths	8.04	7.70	7.58	7.49	7.47
q1 Cancer Deaths	7.80	7.53	7.38	7.30	7.27

* All women are assumed to be followed until age 100 or death.

† Among women who are screened every 3 years until age 65, the number of false positives, colposcopies, CIN 2–3s, cancer cases and cancer deaths are 273.44, 590.30, 63, 11, 2.5 respectively.

Table 5

Expected false-positives, colposcopies, CIN 2–3s, cancer cases and cancer deaths per 1000 women associated with different ages to end screening (varied in five year increments from age 65 to 90). Women are assumed to have been screened every 3 years to age 65. Thereafter, they are screened until age 70, 75, 80, 85 or 90. Screening intervals of every three (q3) or five (q5) years for those who have. *, †

Screening q3 (until Age 65)					
	Age 70	Age 75	Age 80	Age 85	Age 90
q5	False Positives	287.69	300.56	311.67	320.51
q3	False Positives	300.14	323.48	334.08	349.92
Screening q3 (until Age 65)					
q5	Colposcopies	621.45	650.61	676.05	696.34
q3	Colposcopies	648.96	700.23	723.36	758.16
Screening q3 (until Age 65)					
q5	CIN 2–3s	66.05	69.74	73.12	75.85
q3	CIN 2–3s	69.02	74.33	76.62	80.21
Screening q3 (until Age 65)					
q5	Cancer Cases	10.66	9.95	9.46	9.21
q3	Cancer Cases	10.03	9.10	8.80	8.50
Screening q3 (until Age 65)					
q5	Cancer Deaths	2.25	2.00	1.83	1.75
q3	Cancer Deaths	2.03	1.74	1.65	1.55
					1.52

* All women are assumed to be followed until age 100 or death.

† Among women who are screened every 3 years until age 65, the number of false positives, colposcopies, CIN 2–3s, cancer cases and cancer deaths are 273.44, 590.30, 63, 11, 2.5 respectively.

Table 6

Oregon EPC Report-based Estimates (2011). ⁹ Expected false-positives, colposcopies, CIN 2–3s, cancer cases and cancer deaths (per 1000) associated with cytology and HPV test-based strategies either alone or in combination. ^{*}, [†]

Strategy	False Positives	Colposcopies	CIN 2–3s	Cancer Cases	Cancer Deaths
Cytology, q3, Age 21; Cytology and HPV, q5, Age 30	255.35	575.46	84.39	7.44	1.35
Cytology, q5, Age 21	213.97	483.36	66.01	12.69	2.71
Cytology, q3; Age 21; Cytology and HPV, q3, Age 30	381.33	824.74	93.10	4.73	0.74
Cytology, q3, Age 21	349.92	758.16	80.21	8.50	1.55
Cytology, q2, Age 21; Cytology and HPV, q3, Age 30	539.64	1129.39	94.39	3.64	0.52
Cytology q2, Age 21	515.26	1083.52	87.52	5.80	0.92
Cytology, q1, Age 21 Cytology and HPV, q3, Age 30	727.22	1488.19	95.19	2.57	0.35
Cytology, q1, Age 21	951.45	1931.00	91.50	2.50	0.32

^{*} Time horizon is a lifetime

[†] Age to begin screening is fixed at age 21. For the combined cytology and HPV strategies, cytology-based screening is assumed prior to age 30, with a repeat cytology test for ASC-US. The strategy of cytology and HPV begins at age 30. Women with normal cytology results and HPV negative results are assumed to be screened every 3 years or every 5 years.

Oregon EPC Report-based estimates (2011).⁹ Sensitivity analysis including a strategy of HPV followed by cytology if HPV positive. Analysis showing expected colposcopies per 1,000 women, incremental colposcopies, life-years (LYs), incremental LYs, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21. Screening intervals of every one (q1), two (q2), three (q3) and five (q5) years are compared.

Table 7

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
HPV, followed by Cytology, q5, Age 30	234	234	69211.89	195.59	1
HPV, followed by Cytology, q3, Age 30	301	66	69231.50	19.61	3
HPV, followed by Cytology, q2, Age 30	423	122	69239.62	8.12	15
HPV, followed by Cytology, q1, Age 30	643	220	69247.71	8.09	27