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## Original Research Article

# Cost effectiveness analysis of cervical cancer screening in women until age 70

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### ABSTRACT

**Background:** 2017 US Preventive Services Task Force guidelines for screening cervical cancer and pre-malignant lesions advise that screenings cease for women over age 65, with qualifications. Recent literature has identified significant discrepancies in rates of cervical cancer in older women – if hysterectomies in this patient population is accounted for, cervical cancer incidence does not decline with age as previously established. This adjusted incidence of cervical cancer necessitates a re-examination of current practice.

**Methods:** This study seeks to demonstrate the utility of extending the cervical cancer screening age recommendations to age 70. Cost effectiveness will be estimated, from a payer perspective, of extending screening to age 70 for the United States women's population in those who have not undergone hysterectomy or otherwise been treated for past cervical cancer or premalignancy. A Markov model was constructed to project outcomes in a hypothetical cohort of 10 000 women aged 65 to 70, with a time horizon of lifetime. A Probability Sensitivity Analysis determined the robustness of the result, and the Incremental Cost-effectiveness Ratio (ICER) is charted.

**Results:** The economic evaluation of screening compared to none in this population was determined to be cost effective, with an ICER demonstrating a cost benefit, and Quality Adjusted Life Year (QALY) benefit, to extended screening.

**Conclusions:** The sensitivity analysis confirms the robustness of this result. Implementing extended screening guidelines could potentially be a significant gain for both patients and society.

**Keywords:** Cancer screening, Cervical cancer, Economic analysis, Gynecology, Primary care, Prevention

### INTRODUCTION

Current guidelines for screening of cervical cancer and pre-malignant lesions advise that screenings cease for the majority of women over the age of 65-those who have not had detectable dysplasia in the previous ten years.<sup>1,2</sup> In the United States, recent literature has identified significant discrepancies in rates of cervical cancer in older women-if hysterectomies in this patient population are properly accounted for, cervical cancer incidence does not decline with age as previously established.<sup>3</sup> This adjusted incidence of cervical cancer necessitates a reexamination of current practice. Miscalculated

incidence rates have left a significant segment of elderly women unscreened, and potentially untreated for cervical dysplasia, and cancer. Subsequently, the impact on healthcare costs, both in health and financially, of this situation has gone unexamined.

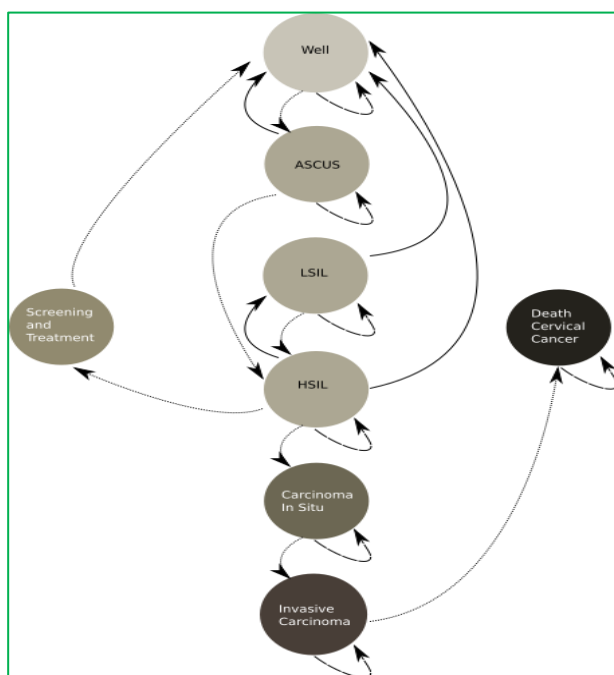
This study examines the cost effectiveness of increasing the current recommended age of screening for cervical cancer up until the age of 70- improved screening guidelines requires evaluation, through incorporation of more accurate epidemiologic data in economic models. The costs of screening every five years with a combination of Papanicolaou cytology test and HPV

DNA test, with subsequent treatment, are considered against the costs of cervical cancer detected at the symptomatic stages at which elderly women would currently present in lieu of screening. Our study investigates the potential cost effectiveness and impact of expanded screening guidelines for the high-risk population of elderly women.

## METHODS

### Model

A Markov model (Figure 1) was constructed to project outcomes in a hypothetical cohort of 10 000 women aged 65 to 70. The model is an appropriately outlined disease progression of cervical dysplasia to either treatment, or to cancer onwards to death due to metastatic disease.



**Figure 1. Markov model, cervical dysplasia, with progression to cancer.**

At the outset, all members of the cohort will be healthy. Transition states will represent the clinical spectrum involved in cervical cancer diagnosis in regard to cytological and clinical stages as outlined by the Bethesda system, terminating with death from cervical cancer, or reversion to a healthy state via positive screening and treatment.<sup>4</sup>

Markov cycles will last 6 months, based upon mean regression times from disease states to a healthy state.<sup>5</sup> Time horizon of the study will be lifetime - current life span is 81 for women in the US, subsequently there will be 32 cycles. Progression of disease states average significantly longer than six months. There will be an absorbing state of death.

### Event probabilities

The Markov model makes necessary concessions to the availability of suitable data used to inform event probabilities. Transitions among pre-cancerous states is as comprehensive as possible-as LSIL and HSIL states are often treated upon detection, there are no directly observed progressions of disease in literature for the population we are examining. Probabilities in these instances were sourced from studies in which transitions were extrapolated from study data of LSIL and HSIL prevalence rates.<sup>6</sup>

Assumed transition states probabilities have been calculated on the basis that each probability should sum to zero-so that the probability that a particular state remains in the next cycle, is the difference between 1 and the probabilities of progression and regression taken from the literature (following correction to the six-month cycle used in the model).

### Costs and preferences

Costs will be considered from a societal perspective and measured in dollars per QALY using established EQ5D scores (Table 1). Costs were derived from the American Medical Association's 2015 CPT Coding guides and are intended to reflect the entirety of payer cost for each state in the Markov model. A discount rate of 1.5% per six-month cycle will be used. Preference weights (Table 1) were taken from studies determining EQ5D scores in regard to specific stages of disease or health as described in the model's states. Refer to Table 1 for the probabilities, costs, and preferences utilized for the study.

### Economic analysis

The Markov model, with aforementioned inputs, produced an Incremental Cost Effectiveness Ratio (ICER), which allows for a direct estimation in real world costs and impacts as to the utility of improved screening guidelines. Costs and preference weights (used to determine QALY's) were placed in the designed Markov model along with the simulated cohort in order to produce a final comparison between the costs and impacts of screening relative to no screening.

### Univariate sensitivity analysis

Selected parameters from the Markov model's costs, preferences, and probabilities were varied in order to determine the effect of potentially plausible variation on the results of the model. Critical values were systematically altered and the resulting ICER values were placed in a tornado diagram to analyze the effect in relation to the base case ICER point estimate and compare the sensitivity of the model to an array of parameter variations.

**Probabilistic sensitivity analysis**

In order to provide the likelihood that the ICER is within an acceptable range, considering the potential variation of

all parameters at once, a cost effectiveness cloud is created.

**Table 1: Base case probabilities, costs, and utility scores.**

Group	Parameter	Base Case	Distribution	Reference
No screening cohort	Probability WELL progresses to ASCUS	0.02070	Uniform	(Edelman, et al) <sup>20</sup>
	Probability WELL stays	0.96710	Uniform	Assumption
	Probability WELL progresses to LSIL	0.01220	Uniform	(Edelman, et al) <sup>20</sup>
	Probability ASCUS progresses to HSIL	0.00450	Uniform	(Walker, et al) <sup>18</sup>
	Probability ASCUS regresses to WELL	0.17048	Uniform	(Melnikow, et al) <sup>21</sup>
	Probability ASCUS stays	0.82503	Uniform	Assumption
	Probability LSIL progresses to HSIL	0.02573	Uniform	(Cantor, et al) <sup>6</sup>
	Probability LSIL regresses to WELL	0.07400	Uniform	(Cantor, et al) <sup>6</sup>
	Probability LSIL stays	0.90027	Uniform	Assumption
	Probability HSIL progresses to CC	0.33533	Uniform	(Rositch, et al) <sup>3</sup>
	Probability HSIL regresses to LSIL	0.01990	Uniform	(Cantor, et al) <sup>6</sup>
	Probability HSIL regresses to WELL	0.08758	Uniform	(Melnikow, et al) <sup>21</sup>
	Probability HSIL stays	0.55720	Uniform	Assumption
	Probability HSIL progresses to S+T	0.00000	Uniform	Assumption
	Probability S+T progresses to WELL	1.00000	Uniform	Assumption
	Probability CC progresses to DEATH	0.01600	Uniform	(Howlader, et al) <sup>22</sup>
	Probability IC stays	0.98400	Uniform	Assumption
	Probability DEATH stays	1.00000	Uniform	Assumption
Screening cohort	Probability WELL progresses to ASCUS	0.02070	Uniform	(Edelman, et al) <sup>20</sup>
	Probability WELL stays	0.97930	Uniform	Assumption
	Probability Well progresses to LSIL	0.01220	Uniform	(Edelman, et al) <sup>20</sup>
	Probability ASCUS progresses to HSIL	0.00450	Uniform	(Walker, et al) <sup>18</sup>
	Probability ASCUS regresses to WELL	0.17048	Uniform	(Melnikow, et al) <sup>21</sup>
	Probability ASCUS stays	0.82503	Uniform	Assumption
	Probability LSIL progresses to HSIL	0.02573	Uniform	(Cantor, et al) <sup>6</sup>
	Probability LSIL regresses to WELL	0.07400	Uniform	(Cantor, et al) <sup>6</sup>
	Probability LSIL stays	0.90027	Uniform	Assumption
	Probability HSIL progresses to CC	0.01053	Uniform	(Rositch, et al) <sup>3</sup>
	Probability HSIL regresses to LSIL	0.01990	Uniform	(Cantor, et al) <sup>6</sup>
	Probability HSIL regresses to WELL	0.08758	Uniform	(Melnikow, et al) <sup>21</sup>
	Probability HSIL stays	0.00000	Uniform	Assumption
	Probability HSIL progresses to S+T	0.88200	Uniform	Assumption
	Probability S+T progresses to WELL	1.00000	Uniform	Assumption
	Probability CC progresses to DEATH	0.01600	Uniform	(Howlader, et al) <sup>22</sup>
	Probability IC stays	0.98400	Uniform	Assumption
	Probability DEATH stays	1.00000	Uniform	Assumption
Costs (All)	Cost Well	0.00000	Fixed	Assumption
	Cost No Screening (ASCUS, LSIL, HSIL)	0.00000	Fixed	Assumption
	Cost to screen	122.60	Gamma	(Medicare) <sup>23</sup>
	Cost colposcopy and treatment	11928.00	Gamma	(Medicare) <sup>23</sup>
	Cost cervical cancer treatment	25200.00	Gamma	(Subramanian, et al) <sup>24</sup>
Preferences (All)	Well/Undiagnosed LSIL/ASCUS/HSIL	0.88000	Triangular	(Kind, et al) <sup>11</sup>
	Diagnosed ASCUS/LSIL	0.85000	Triangular	(Zhang, et al) <sup>25</sup>
	Diagnosed HSIL	0.85000	Triangular	(Zhang, et al) <sup>25</sup>
	Screening + Treatment	0.73000	Triangular	(Zhang, et al) <sup>25</sup>

Multiple iterations are simulated of the cohort progressing through the model, along with simultaneously altered probabilities, preferences, and costs. The cloud is then utilized to produce a cost effectiveness curve, which graphically indicates the likelihood that the result is cost effective, in relation to societal willingness to pay at a certain dollar value. Finally, the net monetary benefit chart is created by converting the realized health benefits by the cost, then with the cost benefit subtracted, which displays, along with a confidence interval, the benefit that can be realized at dollar values of willingness to pay.

## RESULTS

The economic, base case analysis (Table 2) determined that screening in the study population dominates the alternative of no screening, demonstrating both lower average cost, and higher average quality of life.

The per person, calculated difference for screening over none, shows to be a 0.3 QALY improvement, as well as a \$5,402 reduction in costs, after accounting for time discount.

**Table 2: Base case analysis.**

	Not discounted			Discounted		
	Screening	None	Difference	Screening	None	Difference
Cost	4853.9	13929.2	-9075.3	3595.8	8997.8	-5402.0
QALYs	28.0	27.6	0.4	21.1	20.8	0.3
ICER			(21 050)			(19 578)

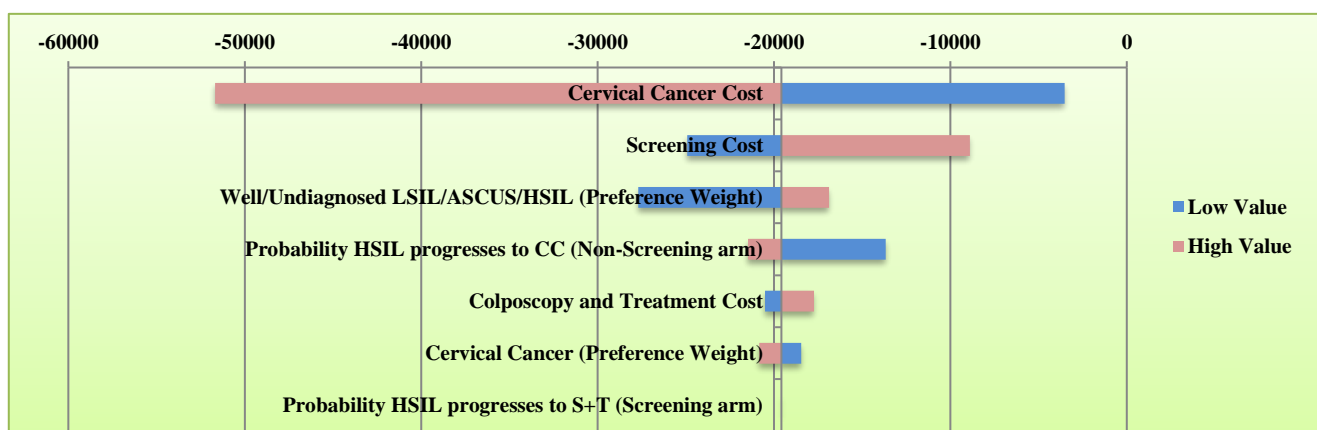
### Sensitivity analysis

Univariate (Table 3) and multivariate sensitivity analyses were carried out on the model and its parameters. The

model demonstrated significant robustness of the base case point estimate ICER, as both the univariate tornado diagram (Figure 2), and probabilistic sensitivity analyses showed a consistent maintenance of both the cost benefits and health benefits of the screening intervention.

**Table 3. Univariate sensitivity analysis.**

Parameter	ICER		Difference in ICER
	Low Value	High Value	
Well/Undiagnosed LSIL/ASCUS/HSIL (Preference Weight)	-27686	-16881	10805
Cervical Cancer (Preference Weight)	-18460	-20839	2379
Probability HSIL progresses to CC (Non-Screening arm)	-13672	-21476	7804
Probability HSIL progresses to S+T (Screening arm)	-19579	-19576	3
Cervical Cancer Cost	-3524	-51685	48161
Screening Cost	-24916	-8900	16016
Colposcopy and Treatment Cost	-20504	-17725	2779



**Figure 2. Tornado diagram of univariate analysis.**

Critical selected parameters for the univariate analysis indicated the greatest sensitivity of the model to the costs of cervical cancer and of screening. However, even with plausible variation of costs, with an extended upper limit, the intervention remained cost effective.

This is visible on the tornado diagram, where ICER variation due to parameter variation is illustrated around the study point estimate. Multivariate analysis involved a

probabilistic sensitivity analysis that allowed concurrent variation of parameters across the model. A thousand simulated iterations, utilizing the estimated variation of each parameter, of the model produced a cost effectiveness cloud (Figure 3) with 87.1% of estimated ICER's falling within the fourth quadrant. The cost effectiveness curve (Figure 4) demonstrated a likelihood of cost effectiveness of 0.81 even at a willingness to pay of 0 dollars, with a 0.91 likelihood from \$10,000 onwards.

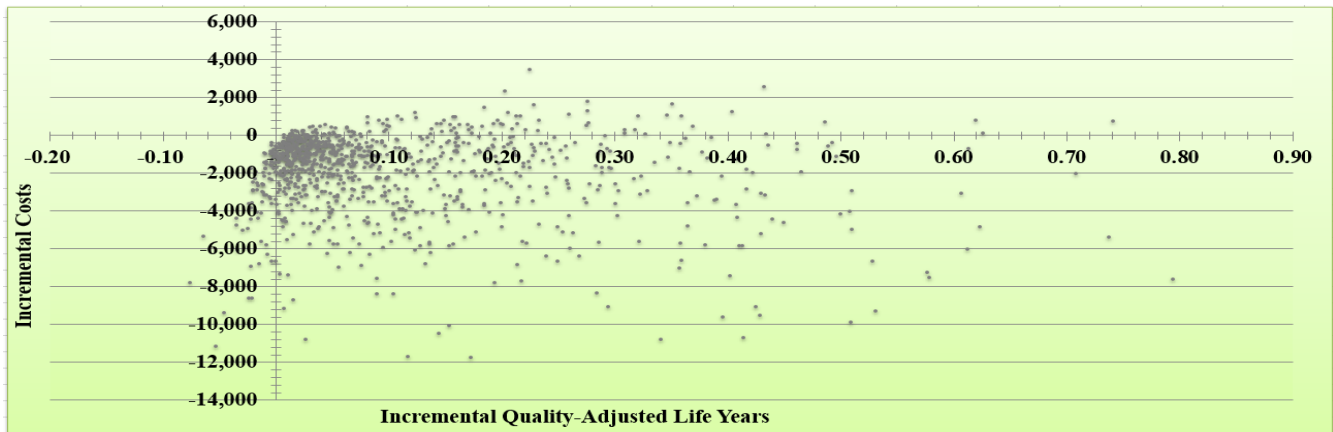


Figure 3: Scatterplot of probabilistic sensitivity analysis simulation.

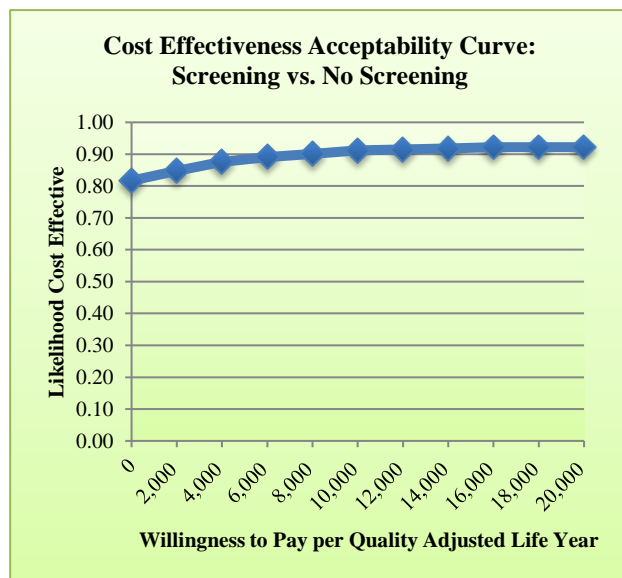


Figure 4. Cost effectiveness acceptability curve from probabilistic sensitivity analysis.

Lastly, the net monetary benefit (Figure 5) shows an NMB of \$2000 - \$3000 across a willingness to pay of 0 to 20,000 dollars. The 68% confidence interval (one standard deviation above and below the estimated line of NMB) remains positive above a \$2000 willingness to pay.

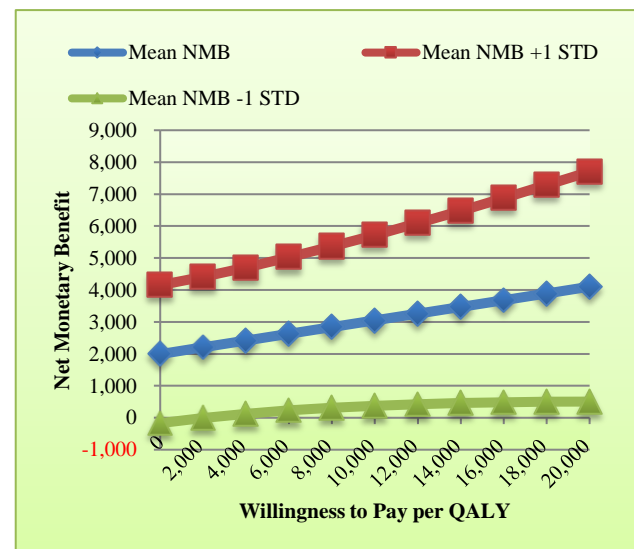


Figure 5. Net monetary benefit as a function of willingness to pay per QALY-screening relative to no screening.

## DISCUSSION

### Findings

The conducted cost effectiveness analysis determined that continued screening for cervical cancer in elderly women



up to the age of 70 is cost effective, with both an improvement in costs and in health outcomes, therefore dominating the current practice of no screening. This finding is supported by demonstrated robustness through both univariate and multivariate sensitivity analysis, indicating that cost effectiveness holds true over a range of possible costs, disease and treatment probabilities and societal preferences for included health states.

### **Strengths and limitations**

The study provides a straightforward, and concise analysis of screening effects on cervical cancer impacts through its practical disease progression and treatment Markov model. The model only takes into account states that can be accounted for with probabilities in literature reporting from clinical observations. Thus, the effect of lengthened screening guidelines, as well as the effect of the sensitivity analyses, are understandably plausible.

The main strength of the study lies in its use of the most current epidemiological data as reported by Rositch.<sup>3</sup> Cost effectiveness can only be as precise and applicable as the data that informs its analysis and conclusions, and for this study, Rositch's revealing findings on the incidence of cervical cancer in the elderly female population in the United States are key to determining the cost effectiveness of screening in the same population.

The short time span of the study allowed the investigator to omit a model stage accounting for deaths from other causes (besides cervical cancer). However, considering the elderly age of the population in question, there remains a likelihood that death from other causes could have an effect upon the outcomes of the analysis run through said model. This should be considered when applying the findings to clinical practice, although the simplicity of the model does help insure its internal validity.

Other concerns, as in many other cost effectiveness studies utilizing secondary data, is the consistency of input costs, probabilities and preference weights. Costs, fortunately, are all sourced from the American Medical Association, are updated yearly, and are intended to represent the entirety of payer cost. Consistent probabilities inputs are much more challenging to find, and unfortunately are derived from multiple sources, and synthesized in order to be representative of the same time span across the model. Likewise, with preference weights, which come from studies on different populations. These are debatable, but unavoidable weaknesses, that the study team has sought to mitigate through considerable discretion on their selection and use.

### **Policy implications**

The most immediate concern regarding the findings is to inform the stated medical practice guidelines currently

being utilized in the US today. Given the startling difference in Dr. Rositch, and team's findings regarding the incidence of cervical malignancy given corrections for hysterectomies in the same population, it is not unexpected to find that screening, up until the age of 70, is forecast to produce such a dramatic impact. Consequently, this study's cost effectiveness data requires reconciliation with policy maker considerations, to potentially effect a change on the current screening only until age 65 guidelines.<sup>1,2</sup> Furthermore, findings of the sensitivity analysis provide strong support for the likelihood of a positive impact of improved screening, even if moderate changes to costs or preferences in regard to cervical cancer and medical care occur. This can be regarded as a continuation of the effort of implementing prevention as intervention in the modern medical practice.

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