eAppendix

Introduction

In this study, we evaluated the cost-effectiveness of cervical cancer screening compared with the status quo. Cost-effectiveness analysis is a type of decision analysis that compares the relative health and economic consequences of different interventions (including no intervention). Decision-makers can assess the cost incurred to achieve a unit gain of health improvement. The rationale behind cost-effectiveness analysis is that resources are limited, and thus, should be used as efficiently as possible to maximize health benefits. Cost-effectiveness analysis helps policymakers maximize population health and studies are conducted based on a societal perspective, which requires decision makers to incorporate all direct and indirect costs and health benefits associated with an intervention.

We developed a microsimulation model of cervical cancer to conduct the cost-effectiveness analysis. Although empirical studies based on actual data may produce reliable findings, they are costly or may not be useful or able to assess long-term impacts. Simulation modeling, however, is a more flexible, cost-effective approach to conducting economic evaluation to help inform decision-making compared with studies based on actual behavioral observations. By incorporating the best available biological, clinical, and epidemiological evidence, our simulation model of cervical cancer enables us to simulate a population of interest; capture the disease progression of each individual; predict the long-term consequences of different interventions in a virtual environment; and provide insight into the cost-effectiveness of the interventions. We refer to Goldie et al for a more comprehensive discussion on the use of simulation modeling to inform policymaking for cervical cancer prevention.[1] This technical report provides details about our model.

Natural History Model

The natural history of cervical cancer was modeled using 16 states, including well; HPV infection; low- and high-grade squamous intraepithelial lesions (SIL); hysterectomy for benign disease; undetected and detected cervical cancer states I-IV; survival from cancer; and death due to cervical cancer or other causes (**eAppendix Figure 1**). Transitions between health states were governed by transition probabilities that depend on age, SIL level, cancer stage, and screening or vaccination strategies. We used 1 year as a basic cycle length.

Each year, women in the simulated model could be infected with HPV or stay uninfected. We assumed all cases of cervical cancer start from HPV infection, which is consistent with the epidemiologic finding that HPV causes the majority of cervical cancer cases.[2,3] HPV infection, clearance, and progression to low- or high-grade SIL is a complex process that varies, depending on HPV virus type and patient characteristics, such as age and immune status. We used average transition probabilities for all virus types and thus, we did not need to distinguish different types of HPV.

This simplified our model without losing important information. We modeled the incidence of HPV infection as a function of age, and assumed the incidence function did not change throughout the simulation.

Women infected with HPV can regress to infected, stay unchanged, or progress to low- or high-grade SIL. Similarly, women with low-grade SIL can undergo regression to uninfected or infected, no change, or progression to high-grade SIL. Women with high-grade SIL can regress, stay the same, or progress to stage 1 cancer without symptoms. Current knowledge about the natural history of cervical cancer suggests that most HPV infections will regress on their own without any treatment, as some persistent HPV infections may progress to high-grade SIL and eventually, cervical cancer.[4,5]

Women in stage 1 cancer without symptoms either become symptomatic or progress to higher stages of cancer without detection. Once cancer becomes symptomatic or is detected by screening, the patient will undergo medical treatment. Both the probability of survival and the probability of mortality due to cancer are stage-specific; a higher stage of cancer will typically result in lower probability of survival with or without treatment, and a higher mortality rate.

Women without cancer have age-specific probabilities of undergoing a hysterectomy due to other causes.[6] It is important to include hysterectomy in the model because it will significantly alter the natural history of cervical cancer. In addition, all women could die due to other causes other than those included in this study. We use age-specific mortality rates from national vital statistics data.[7]

We assumed that women in our studied population received their screening tests (Pap tests) at the appropriate interval, and also received appropriate diagnostic procedures (eg, colonoscopy and biopsy) and treatment based on the results of the screening tests. Specifically, women with low-grade SIL were re-examined every 6 to 12 months until they had 3 negative screening test

results.[8] In addition, women with confirmed high-grade SIL or cancer were treated according to published guidelines.[8]

Parameter Estimation

Incidence of HPV infection. The probabilities for HPV incidence, regression, and progression were based on averages for all virus types given that our model did not distinguish between different types of the HPV virus.[9] **Table 1** of the eAppendix presents the age-specific estimates for HPV incidence. The table shows HPV incidence reaches a peak from age 17 to 21, which is consistent with the epidemiologic finding among women nationwide. Note that our model would have more accuracy if we could use population-specific HPV incidence rates, but these data are not available for the study.

Transition probabilities among precancerous states. We obtained age-specific annual transition probabilities among precancerous states from published literature.[6,9,10] **Table 2** of the eAppendix presents parameter values and the corresponding literature sources. The table shows that the majority of women infected with HPV will regress, and only a small proportion will progress every year.

Also, the regression rates decrease significantly as age increases. Women with high-grade SIL who are older than 30 years have an average of 4 times higher greater probability of progressing to cancer compared with women with high-grade SIL who are younger than 30 years. These data are also in consistent with the Surveillance, Epidemiology, and End Results (SEER) data.[11]

Transition probabilities among cancer states. Women with asymptomatic cervical cancer have a stage-specific probability of having symptoms and progressing to the more advanced cancer stage (eAppendix Table 3). It is evident that a more advanced cancer stage is associated with a greater likelihood of symptoms. For example, the annual probability of symptom onset ranges from 0.15 for stage 1 cancer to 0.9 for stage 4 cancer. Table 3 of the eAppendix also presents probabilities of death due to cancer, which is a function of both cancer stage and years following diagnosis. The parameters were originally estimated from the SEER data collected from the National Cancer Institute, and were also used in other studies.[9-11] We assumed that there was no mortality due to cancer after 5 years postdiagnosis. This assumption was consistent with other cost-effectiveness

analysis studies and clinical findings.[9,10,12] We estimated age-specific female mortality rates due to other causes by subtracting age-specific mortality rates due to cervical cancer from age-specific all- cause mortality rates obtained from the US life tables in 2010.[7]

Quality of life weights. We used quality of life weights (QALYs) to measure the effectiveness of different prevention programs in preventing cervical cancer. We not only considered morbidity and mortality when calculating QALYs, but also incorporated the effect of aging. For example, a healthy woman who is less than 20 years old has a quality of life weight of 1, and a healthy woman older than 79 years has a quality of life weight of 0.724. We obtained the age-specific quality of life weights based on nationally representative values.[16] When a woman had cancer, her quality of life weight would be determined based on her cancer stage rather than her age. We obtained the stage-specific QOL weights from published studies.[14,15] The QOL weight is 0 when a person is in a death state. Table 4 of the eAppendix presents the age- and stage-specific estimates of QOL weights.

Costs and other parameters. Cost calculation in our model includes both program costs and treatment costs (eAppendix Table 5). Specifically, the screening program costs $311 per person. We calculated this figure by adding up all costs incurred in the program ($1,399,815), including Pap test costs, program staff salaries, and health promotion media and outreach cost, and dividing the total cost by the number of women (4500) who received screening. We estimated annual treatment costs for high-grade SIL, local cervical cancer (stage 1), regional cervical cancer (stages 2 & 3), and distant cervical cancer (stage 4) from published literature.[16-19] Women with HPV infection or low-grade SIL do not treatment and thus, do not incur additional costs.

Table 5 of the eAppendix also includes other parameters required to assess the cost-effectiveness of different prevention programs. In particular, we estimated the screening test characteristics (sensitivity and specificity) from published literature.[15,20,21] Although we expect that the prevalence of HPV infection in Bexar County is higher than the national average, we still used the national average (26.8%) in our model due to a lack of population-specific data.[4] Finally, we discounted both costs and QOL by 3% annually.

User Interface

Figures 2 and **3** of the eAppendix demonstrate the model input and output interfaces. The input interface enables users (eg, policymakers) to easily assess the cost and effectiveness of either *A Su Salud* Pap screening program or HPV vaccination program for a user-defined length of time. Through the input interface, users can perform "What if" analyses by varying age distribution, prevalence of HPV infection for the initial population, probabilities of receiving Pap tests or HPV vaccinations, and the per capita cost of each program. This feature is especially useful when there are uncertainties in the estimation of parameters. The output interface enables users to visualize dynamic changes of several simulation outcomes, including yearly prevalence of HPV, incidence of low- and high-grade SIL, cancer incidence and mortality, and cost and effectiveness measures (ie, mean cost, mean QALY, life expectancy).

Comparing simulated time series data with actual time series statistics would help to conceptually validate model predictions and calibrate model parameters. We designed the user-friendly interfaces so that the cervical cancer prevention economic evaluation model could be readily used when there are updates to the screening and vaccination parameters or the program is implemented in another population.

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1.

eAppendix Table 1. Age-Specific Annual Incidence for HPV Incidence[4]

Age	Value
12	0
13	0.01
14	0.05
15	0.1
16	0.1
17	0.12
18	0.15
19	0.17
20	0.15
21	0.12
22	0.1
23	0.1
24-29	0.05
30-49	0.01
50	0.005

HPV indicates human papillomavirus.

eAppendix Table 2. Annual Transition Probabilities Among Precancerous States

Parameter	Age	Value (transition	Source
HPV to Well	15-24	0.552	4,5
	25-29	0.37	
	30-39	0.175	
	40-49	0.103	
	50+	0.034	
HPV to Low-grade SIL	--	0.054	
HPV to High-grad SIL	--	0.006	
Low-grade SIL to Well	15-34	0.09	
	35+	0.054	
Low-grade SIL to HPV	15-34	0.01	
	35+	0.006	
Low-grade SIL to High-grade	15-34	0.02	
	35+	0.06	
High-grade SIL to Well	--	0.03	
High-grade SIL to Low-grade	--	0.03	
High-grade SIL to Cancer	12-29	0.01	
	30+	0.04	
Well, HPV, Low- and High-grade SIL to Hysterectomy	18-44	0.005	10
	45-64	0.006	
	65+	0.002	

HPV indicates human papillomavirus; SIL, squamous intraepithelial lesions.

eAppendix Table 3. Annual Transition Probabilities Among Cancer States and Mortality Rates

Parameter	Value	Source
Probability of symptoms for Cancer stage 1	0.15	[4,5]
Probability of symptoms for Cancer stage 2	0.225	
Probability of symptoms for Cancer stage 3	0.6	
Probability of symptoms for Cancer stage 4	0.9	
Cancer Stage 1 to Cancer stage 2	0.438	
Cancer Stage 2 to Cancers stage 3	0.536	
Cancer Stage 3 to Cancer stage 4	0.684	
Mortality rates for Cancer stage 1		
Year 1	0.014	
Year 2	0.042	
Year 3	0.062	
Year 4	0.071	
Year 5	0.087	
Mortality rates for Cancer stage 2 & 3		
Year 1	0.138	
Year 2	0.292	
Year 3	0.379	
Year 4	0.438	
Year 5	0.464	
Mortality rates for Cancer Stage 4		
Year 1	0.484	
Year 2	0.698	
Year 3	0.78	
Year 4	0.834	
Year 5	0.842	
All-cause mortality rates for women	Age-Specific	[11]

eAppendix Table 4. Estimates of Quality of Life Weights

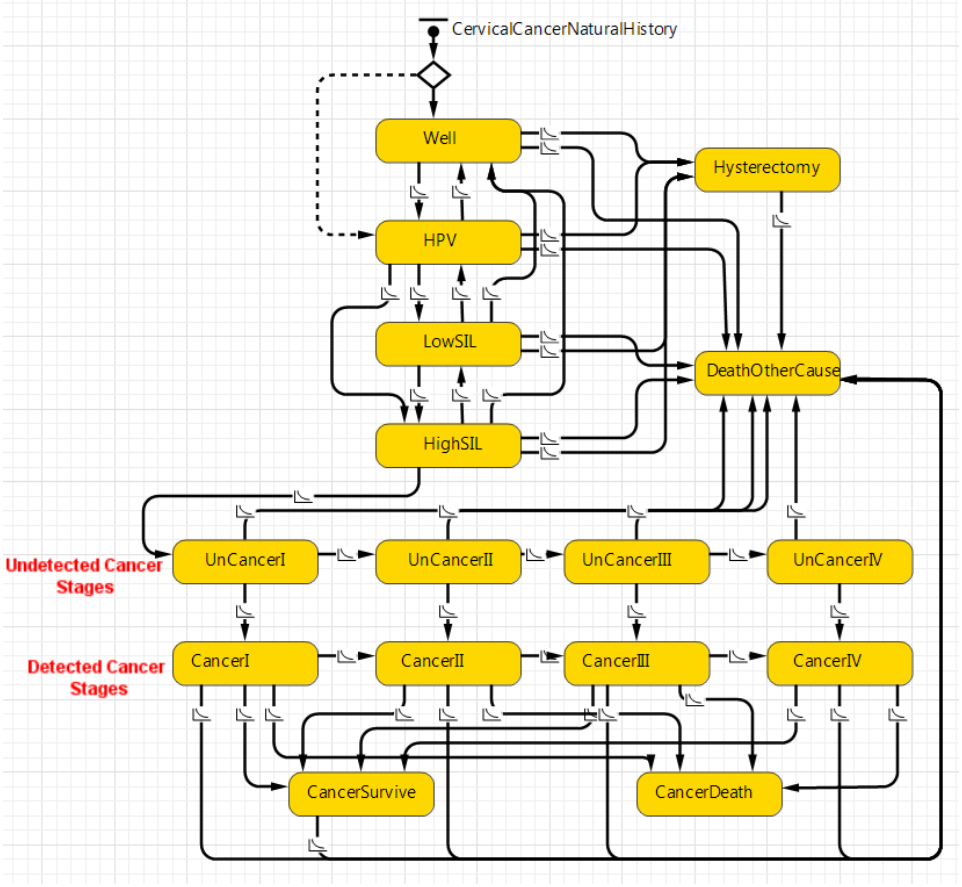
Parameter	Value	Source
Quality weights by age for people without cancer		[16]
<20 year	1.000	
20-29 year	0.913	
30-49 year	0.893	
50-59 year	0.837	
60-69 year	0.811	
70-79 year	0.771	
>79 year	0.724	
Quality weights by cancer stage		[13,17]
Local cervical cancer (stage 1)	0.680	
Regional cervical cancer (stages 2 & 3)	0.560	
Distant cervical cancer (stage 4)	0.480	

eAppendix Table 5. Estimates of Cost and Other Parameters

Parameter	Value	Source
Program cost ($/person)		Program data
Pap test screening	311	
Treatment cost ($ /(person x year))		[18–21]
High-grade SIL	3,221	
Local cervical cancer (stage 1)	24,477	
Regional cervical cancer (stages 2 & 3)	26,197	
Distant cervical cancer (stage 4)	41,959	
Other Parameters		
Screening test characteristics		[13,22,23]
Sensitivity	80%	
Specificity	95%	
Probability of Pap test screening		Program data
Status quo	65%	
Program	80%	
Age distribution	Program-specific	[2]
Prevalence of HPV infection	26.8%	[8]
Discount rate for costs and quality of life weights	3%	

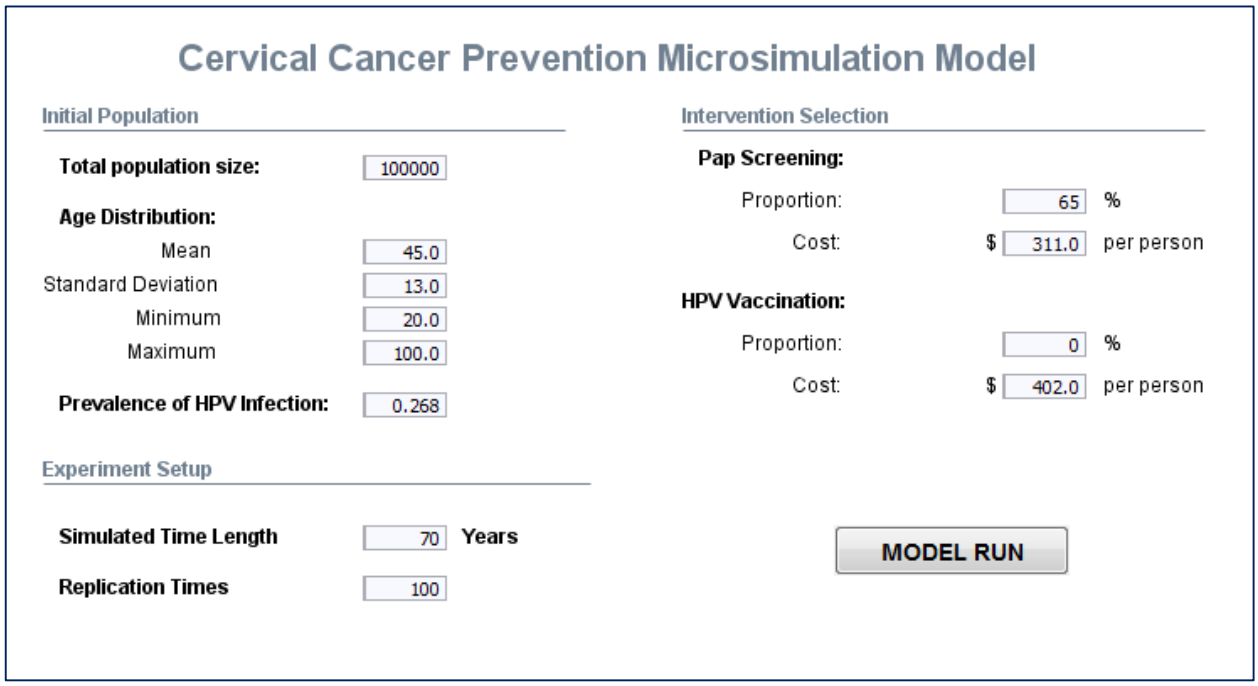
HPV indicates human papillomavirus.

eAppendix Figure 1. Natural History of HPV Infection and Cervical Cancer



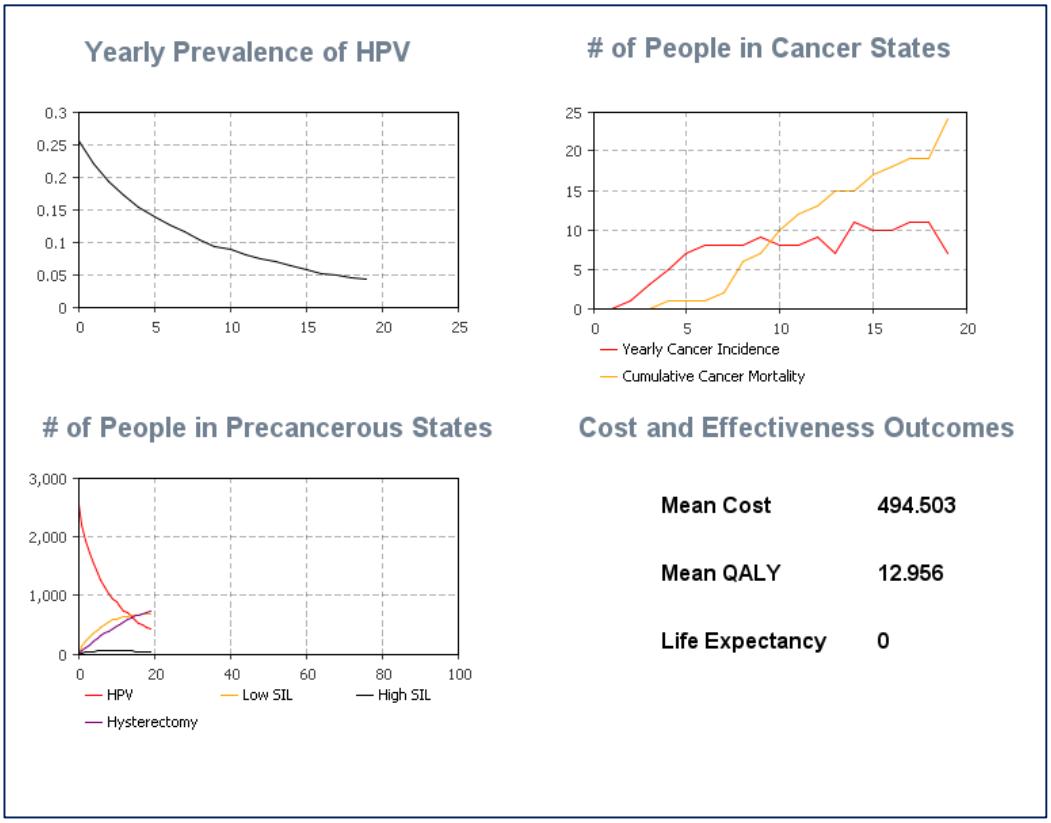
HPV indicates human papillomavius; SIL, squamous intraepithelial lesions.

eAppendix Figure 2. Cervical Cancer Microsimulation Model Input Interface



HPV indicates human papillomavirus.

eAppendix Figure 3. Cervical Cancer Microsimulation Model Output Interface



HPV indicates human papillomavirus; QALY, quality-adjusted life-year.