**Technical Appendix**

The appendix provides additional model details and input data of some important parameters.

**1 Sub-model of cervical cancer and its connection with major model:**

Undetected stage III or higher

Detected stage I

Detected stage II

Detected stage III or higher

Undetected stage II

Undetected stage I

Survivor

Undetected CIN

Detected CIN

**Figure a.1**

The sub-model of “cancer” is a complex state that consists of several subsequent processes. Figure a.1 above illustrates possible subsequent processes of a cervical cancer following a HPV infection and how the sub-model is connected to the three major states (i.e.. H, I and D) in the simulation model. In this study, we separate HPV 16 and HPV 18 infections. It is assumed that either of the two subtypes can independently progress to a pre-cancer stage. A woman’s pre-cancer or in situ cervical cancer stage is defined as a composite state including cervical intraepithelial neoplasia (CIN) 1, CIN 2 or CIN 3, which may progress to an invasive cancer (stage I or higher). CINs can be detected by regular preventive screening, such as pap test. We assume detected CINs will always be treated and go back to the loop of the major simulation model if the patient is not dying in the current epoch. After a regression or treatment, a woman’s HPV may clear or persist, depending upon the annual regression rate of HPV (Sanders and Taira 2003). We use the estimates of naturally acquired HPV immunity reported by Matthijsse et al. (2015) to calculate a woman’s immunity after her HPV clearance. Table a.1 explains all possible transitions between the sub-model and major model.

**Table a.1**

|  |  |
| --- | --- |
| **Transition** | **Significance** |
| Undetected CIN to H | Undetected CIN spontaneously regress and HPV persists |
| Undetected CIN to I | Undetected CIN spontaneously regress and HPV clears |
| Detected CIN to H | CIN is treated and HPV persists |
| Detected CIN to I | CIN is treated and HPV clears |
| H to detected CIN | HPV develops to CIN and CIN is detected by regular screening  |
| H to undetected CIN | HPV develops to CIN and CIN is undetected |

Once a woman’s HPV develops to CIN—either detected or undetected, she enters the “cancer” sub-model. A woman with CIN or invasive cervical cancer may or may not be diagnosed by the regular screening and following colposcopy. The probability is determined based upon the specificity and sensitivity of pap test. We use the accuracy data of pap test, HPV test and colposcopy compiled by Adriana Ley-Chavez (2012) to model the possibility of diagnosis in different states. We assume that women in the simulation model follow the cervical cancer screening guideline of the American College of Obstetricians and Gynecologists (ACOG). Women aged 21–29 years have a Pap test alone every 3 years. And women aged 30–65 years have a Pap test and an HPV test every 5 years (Perkins et al. 2020). In our simulation model, women undergo triannual screening until age 29 and then switch to screening every five years. As a stopping criterion suggested by the ACOG, women will no longer have cervical cancer screening after age 65 years if they never enter the “cancer” sub-state and have two negatives in the most recent two tests. A false negative screening result or a year with no scheduled screening results in the risk of letting a CIN or invasive cancer progress to their next stage. Due to the imperfect accuracy and varying frequency of the screening methods, a CIN may or may not progress to stage I, stage II and finally stage III cancer or higher, if the woman is not dying from cervical cancer or other causes during the process.

We leverage the annual transition rates between different cancer stages reported by Elbasha et al. (2007) to model progressions and regressions between a stage and its adjacent stages. Since our study combine CIN 1, 2 and 3 into a composite CIN state, the annual progression rate from CIN to Stage I is calculated by averaging the annual progression rates of CIN 1 to Stage I, CIN 2 to Stage I and CIN 3 to Stage I weighted by the age-specific prevalence of the three stages of CIN. The annual regression rate from CIN to no lesion is calculated in a similar manner. We assume that regressions only occur in CIN stage. Regressions in invasive stages are not considered in the model.

The transitions between “detected” and “undetected” states is controlled by the frequency and accuracy of the regular screening except for stage III or higher cervical cancer. In addition to the regular screening, a woman with invasive cervical cancer has a certain possibility of developing symptoms, which also results in a transition from “undetected” to “detected” (Elbasha et al. 2007). We assume a woman developing stage III or higher cervical cancer will immediately enter the stage of “detected stage III or higher”, as cervical cancer at this stage is mostly seriously symptomatic.

After treatment, a woman with invasive cervical cancer enters the absorbing state “survivor” and is assigned a stage-specific lump-sum life expectancy. We use the DEALE method along with the 5-year survival of invasive cervical cancer to calculate the lump-sum values (Beck et al. 1982; Howlader et al. 2013 ).

The death rate in the sub-model is calculated based upon both stage-specific annual cervical cancer mortality rates and all-cause death rate of the general population including or excluding cervical cancer-related deaths (Elbasha et al. 2007).

Figure 2.a illustrates how the different invasive cancer stages are transitioning over time in the sub-model.

**Figure a.2 Transitions in the Sub-Model**

**2 Values of the major parameters in the simulation model**

|  |  |  |
| --- | --- | --- |
| **Probability** | **Relevant inputs for base-case estimate** | **Source** |
| $$P\_{t}(H|S)$$ | Base case values are determined by the HPV risk model in Section 2.2 | Model specification |
| $$P\_{t}(S|H)$$ |  Annual HPV 16/18 regression rate by age group* Age 0–24: 45.7%
* Age 25–29: 32.9%
* Age 30+: 6.8%

Naturally acquired HPV immunity after HPV infection* HPV 16: 20%
* HPV 18: 50%
 | * Sanders and Taira 2003

Matthijsse et al. 2015 |
| $$P\_{t}(I|H)$$ |  |  |
| $$P\_{t}(C|H)$$ | CIN incidences in the presence of HPV 16 or 18* CIN 1: 9.4%
* CIN 2: 5.8%
* CIN 3: 3.5%
 | Elbasha et al. 2007 |
| $$P\_{t}(D|C)$$ | Stage-specific cervical cancer annual death rate by age group

|  |  |  |  |
| --- | --- | --- | --- |
|  | Stage I | Stage II | Stage III or higher |
| <=29 | 0.7% | 13.4% | 42.9% |
| 30-39 | 0.6% | 8.9% | 41% |
| 40-49 | 0.8% | 11% | 46.7% |
| 50-59 | 1.9% | 10.1% | 52.7% |
| 60-69 | 4.2% | 17.6% | 54.6% |
| >=70 | 11.6% | 28.6% | 70.3% |

 | Elbasha et al. 2007 |
| $$P\_{t}(D|I)$$ | Refer to *Life table for females: United States, 2012* | Arias et al. 2016 |
| $$P\_{t}(D|H)$$ |  |  |
| $$P\_{t}(D|S)$$ |  |  |
| $$P\_{t}(I|S)$$ | 100% at specified vaccination age, and 0% at other ages | Model specification |
| $$P\_{t}(S|I)$$ | Vaccine protection: 100% ( 80% or 50% in scenarios of sensitivity analysis)  | Assumption |
| $$P\_{t}(H|C)$$ | Probability of HPV persistence after CIN treatment: 10%CIN incidences in the presence of HPV 16 or 18* CIN 1: 9.4%
* CIN 2: 5.8%
* CIN 3: 3.5%

Regression of CINs (to normal)* CIN 1: 32.9%
* CIN 2: 21%
* CIN 3: 13.3%

Annual HPV regression rate by age group* Age 0–24: 45.7%
* Age 25–29: 32.9%
* Age 30+: 6.8%

Naturally acquired HPV immunity after HPV infection* HPV 16: 20%
* HPV 18: 50%
 | Sanders and Taira 2003Elbasha et al. 2007Matthijsse et al. 2015 |
| $$P\_{t}(I|C)$$ |  |  |

**3 Values of the major parameters in the HPV Risk Model**

**Input data for marital status modeling**

Refer to the data compiled by Ley-Chavez (2012)

**Input data for ratio of family income to poverty modeling**

Refer to the data compiled by Ley-Chavez (2012)

**Input data for parity modeling**

The parity in this study is defined by a binary variable indicating if a woman has had live birth, which is determined by the probability of already having first birth (US Census Bureau 2017). The probability is stratified by three factors: age, marital status and race.

|  |  |
| --- | --- |
|  | Probability of already having 1st birth |
| .Women Ever Married | white | African American | Asian |
| ...20 to 24 years | 56.9% | 57.5% | 58.9% |
| ...25 to 29 years | 65.8% | 79.3% | 37.3% |
| ...30 to 34 years | 80.0% | 84.4% | 75.2% |
| ...35 to 39 years | 88.8% | 88.6% | 84.8% |
| ...40 to 44 years | 90.7% | 93.1% | 86.2% |
| ...45 to 50 years | 87.3% | 88.8% | 86.2% |
| .Women Never Married |  |  |  |
| ...20 to 24 years | 15.9% | 27.6% | 5.9% |
| ...25 to 29 years | 27.0% | 51.0% | 11.5% |
| ...30 to 34 years | 40.9% | 67.7% | 21.7% |
| ...35 to 39 years | 47.1% | 74.0% | 33.0% |
| ...40 to 44 years | 50.7% | 74.7% | 35.0% |
| ...45 to 50 years | 43.2% | 75.6% | 28.1% |

**Input data for alcohol use modeling**

The shifts between the three types of drinking behavior are modeled based on data reported by Molander et al.’s 11-year longitudinal analysis (2010).We assume the probability of a transition from one behavior to another behavior is equally distributed in the eleven years and calculate the 11th root of the matrix to get the yearly transition rates.

|  |  |
| --- | --- |
|  | **Terminal type** |
| **Initial type** | non-drinker | moderate drinker | heavy drinker |
| non-drinker | 71.11% | 27.94% | 0.95% |
| moderate drinker | 19.24% | 73.31% | 7.44% |
| heavy drinker | 11.73% | 49.38% | 38.89% |

**Input data for smoking behavior change modeling**

The recent smoking cessation rate reported by the Centers for Disease Control and Prevention (2011) to evaluate the yearly likelihood of a smoker to quit smoking.

|  |  |
| --- | --- |
| **Age group** | **Smoking cessation rate** |
| 18-24 | 8.2% |
| 25-44 | 7.1% |
| 45-64 | 4.7% |
| >=65 | 5.3% |

**Input data for lifetime number of sex partners modeling**

A prediction model fit on NHANES 2015-2016 data is used to predict a woman’s possibility of having sex with new partners in the current year. For those who are predicted to have new partners, the specific numbers of their new sex partners are then estimated based on the distribution compiled by Ley-Chavez (2012). The category “3+” actually assigns three new partners to women in the simulation.

|  |  |
| --- | --- |
|   | **Age** |
| **New Partners**  | **18-24**  | **25-34**  | **35-44**  | **45-54**  | **55-64**  |
| 0  | 0.690  | 0.690  | 0.780  | 0.890  | 0.885  |
| 1  | 0.186  | 0.186  | 0.132  | 0.066  | 0.069  |
| 2  | 0.050  | 0.050  | 0.035  | 0.018  | 0.018  |
| 3+ | 0.074  | 0.074  | 0.053  | 0.026  | 0.028  |

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