MODEL PROFILE
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HARVARD SCHOOL OF PUBLIC HEALTH

Important note: This document will remain archived as a technical appendix for publications. New versions will be added periodically as model refinements and updates are completed. The most current version is available at http://cisnet.cancer.gov/profiles. Note that unlike most PDF documents, the CISNET model profiles are not suitable for printing as they are not typically written or read in sequential fashion.

We recommend you let your interests guide you through this document, using the navigation tree as a general guide to the content available.

The intent of this document is to provide the interested reader with insight into ongoing research. Model parameters, structure, and results contained herein should be considered representative but preliminary in nature.

We encourage interested readers to contact the contributors for further information.

Go directly to the: Reader's Guide.

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READER'S GUIDE

Core Profile Documentation

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5-10 minutes. Each contains links to more detailed information if required.

Model Purpose

This document describes the primary purpose of the model.

Model Overview

This document describes the primary aims and general purposes of this modeling effort.

Assumption Overview

An overview of the basic assumptions inherent in this model.

Parameter Overview

Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Component Overview

A description of the basic computational building blocks (components) of the model.

Output Overview

Definitions and methodologies for the basic model outputs.

Results Overview

A guide to the results obtained from the model.

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MODEL PURPOSE

SUMMARY

The Harvard Cervical Cancer Model ("Harvard-CC") simulates human papillomavirus (HPV) infection and possible progression to cervical cancer in order to inform optimal strategies to reduce cervical cancer morbidity and mortality worldwide.

PURPOSE

Harvard-CC is a comprehensive natural history model that guides the development and evaluation of HPV vaccines and cervical cancer screening programs in order to accelerate the implementation of sustainable, cost-effective strategies to reduce morbidity and mortality from cervical cancer. The Harvard-CC model was originally developed to examine US-specific policy questions surrounding cervical cancer screening. Over the years, the model has expanded to address key scientific developments in this field, including the HPV vaccine and new screening technologies. It has also expanded to address global HPV prevention and reduction strategies in an international setting. Using an iterative approach combining empirical data with decision analytic modeling, this model serves as a tool to provide policy makers with evidence on the effectiveness of different prevention and screening for HPV-induced cervical cancer.

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MODEL OVERVIEW

SUMMARY

This section provides an overview of the Harvard-CC model structure and components.

PURPOSE

The (brief) reason for this model's existence. In particular the problem it addresses and questions it attempts to answer. Consider providing a link to the Model Purpose document here.

Harvard-CC is comprised of two distinct models: 1) a dynamic, compartmental model of natural history that simulates the potential health outcomes of nine HPV infection genotypes and HPV sexual transmission between males and females and 2) a static, individual-based model of HPV-induced cervical carcinogenesis. The models can be used as stand-alone models or can be linked to allow for the inclusion of direct and indirect benefits from vaccination, potential synergies between vaccination and screening strategies, and vaccine cross-protection of non-16/18 types.

The purpose of Harvard-CC is to evaluate prevention and screening programs based on their effectiveness, feasibility, sustainability, and affordability of different policy alternatives to reduce the morbidity and mortality of HPV-caused cervical cancer. The Harvard-CC quantifies the long-term health and economic tradeoffs of alternative policies and their relative cost-effectiveness profiles. It provides policy makers with the effectiveness of various prevention and screening strategies to inform health care policy decisions.

BACKGROUND

Harvard-CC has been adapted as research emerges regarding the natural history of HPV infections and progression to cervical cancer. The model simulates a country-specific population of a cohort of females over their lifetime subject to different screening and vaccination strategies. The model is composed of:

1. A **natural history** component that includes: risk factors for cervical cancer (e.g., age of sexual debut), acquisition of type-specific HPV infections (low-risk; high-risk 16; high-risk 18; high-risk 31; high-risk 33; high-risk 45; high-risk 52; high-risk 58; and other high-risk infections), probability of HPV persistence, risk of progression to (regression from) precancerous lesions

(cervical intraepithelial neoplasia grades 2 and 3 (CIN2; CIN3)) and progression to invasive cancer. Women that develop cervical cancer may be detected symptomatically or may progress to a more severe cancer stage. The model is adapted to different epidemiologic settings by fitting (or calibrating) the model using the best available country-specific data, e.g., HPV prevalence, HPV type distribution in CIN 2, CIN3 and cervical cancer.

2. A **cervical cancer prevention strategy** component that includes primary prevention (vaccination) and secondary prevention (screening to detect pre-cancerous cervical lesions with the possibility of treatment for lesions and cancer).

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ASSUMPTION OVERVIEW

SUMMARY

The Harvard HPV Stochastic Model makes several (but necessary) assumptions in each of its components: 1) natural history, 2) screening and treatment, 3) vaccination, 4) costs, and 5) cost-effectiveness analyses.

BACKGROUND

A number of assumptions are necessary for the model. We have adapted our model to numerous countries, each representing a specific epidemiologic background; across these country-specific models, however, we hold a common "base" assumption regarding the natural history of HPV infections and cervical cancer, allowing for variations in the level or magnitude of these probabilities through multipliers. Because of this assumption, a set of common population inputs (baseline probabilities) is used across all country-specific models (e.g., HPV infection incidence and clearance, and development of precancer and cancer, mortality from cancer as well as non-cancer causes), with country-specific multipliers applied to generate outcomes similar to primary epidemiologic data.

ASSUMPTION LISTING

Population Demographics

- We assume birth and mortality rates consistent with US census data available in the Human Mortality Database (formerly Berkeley Lifetables).
- The model starts as a first-order microsimulation of each individual starting at age 9.
- Death is stratified to reflect mortality due to country-specific, age-, sex-, race-adjusted all-causes and invasive cervical cancer; women may die of cancer or of any other cause at any time in life.
- The time horizon of the analysis incorporates each woman's entire lifetime and is divided into equal one-month increments during which women "transition" from one health state to another.

Monthly transition probabilities are a function of baseline probabilities, often duration-based or age- and/or type-specific, calculated from primary data and

published literature, and the application of multipliers, sometimes type-specific, identified through a parameter search strategy that draws sets randomly from uniform distribution

Natural History

- Consistent with the latest scientific evidence that HPV is responsible for all cervical cancer, we assume that invasive cancer may not occur in the absence of infection with an oncogenic HPV type.
- The model simulates the natural history of cervical carcinogenesis, and does not include other outcomes of HPV infection (i.e., anal cancer, head and neck cancer, etc.).
- Natural history includes progression and regression between true health states (normal, type-specific HPV infection, type-specific CIN2 and CIN3, staged and detected/undetected cervical cancer, and death).
- We assume that our probabilities of age-related HPV incidence serve as a proxy for both age and sexual risk in the base case as well as the HPV type distributions among a woman's sexual partner(s).
- The CIN 1 is not an explicit health state in the model; we assume a persistent HPV infections reflect CIN1.
- HPV infections may progress non-sequentially to CIN2 or to CIN3.
- Only CIN2/3 related to high-risk HPV infections may progress to cancer. Once in cancer, a woman may not regress to other health states; she progresses through the stages as long as she is not detected. Once she is detected via symptoms or screening, she does not progress or regress, but remains in the detected stage-specific state on a stage-specific cancer survival curve.
- CIN2 and CIN3 regress to HPV and normal according to user-defined proportions.
- Among women with CIN regression, we assume a proportion will continue to have a detectable HPV infection.
- We allow for multiple, independent infections of multiple HPV types, with each type able to progress and regress independently. However, if a woman develops a type-specific cancer, other concurrent HPV infections and associated precancers are no longer at risk of progressing/regressing.
- Reinfection of the same HPV genotype is possible; however, type-specific natural immunity is induced.

- The model does not currently simulate HIV separately; any deaths attributed to HIV/AIDS are included in non-cancer mortality.
- If a woman with undetected cancer undergoes a hysterectomy, the procedure detects the cancer.
- Cancer mortality is a function of stage, detection status, and duration of cancer, and can be further adjusted by age (via multipliers).

Screening and Treatment

- Our screening strategies vary as a function of:
  - Primary screening test: cervical cytology, HPV DNA test (traditional, rapid, or self-sampled), Visual Inspection with Acetic Acid (VIA) , combinations of these screening tests (i.e. cotesting with cervical cytology and HPV DNA test)
  - Number of clinical visits from initial screening to treatment or management of CIN and cancer
  - Screening frequency
  - Targeted ages (starting age, stopping age, switching of primary screening test at specified age)
  - Specified follow-up and/or triage consisting of more or less intensive screening, "super" screening (increased surveillance due to an abnormal screening result) or "sub" screening (reduced screening due to persistent normal screening result); verified by colposcopy/biopsy)The screening model simulates the detection of HPV DNA and/or lesion as a function of the sensitivity of the test, which can vary by HPV infection or lesion status and possibly age. Test specificity is defined as the probability of having a negative test among people without lesion and/or HPV DNA.
- Compliance may vary by visit, procedure, and prior test result.
- Outside of their regular intervals (i.e., annual screening, triennial screening, etc.), women may be placed on more or less frequent screening schedules following abnormal results.
- Screening tests are always adequate (e.g., does a woman's sample need to be re-collected because the original sample was inadequate for evaluation), meaning sufficient for analysis (subject to compiler switch).
- If colposcopy detects a lesion, a biopsy is automatically performed; if no lesions are found in colposcopy, the woman will not receive a biopsy.

- The "Developing Country" screening strategies, specified by screening once, twice, or three times in a woman's life, do not allow for confirmation of screening test results with colposcopy. These strategies do allow for an "extra visit" (an additional visit if found screen positive), independent of loss-to-follow-up; currently "extra visit" is not activated.
- VIA test characteristics are equal to cytology test characteristics (specificity 95%, sensitivity for CIN1 70%, sensitivity for CIN2/3 and cancer 80%) (cytology test positivity is further stratified by cytology result though given screening strategies, especially in developing countries, may choose to treat all eligible women with a cytology result of ASCUS or worse in a similar manner); rapid HPV test sensitivity 90%, specificity 90%; HPV test sensitivity 100% (for presence of HR HPV and not for presence of CIN) and specificity 100% (for absence of HR HPV).
- In "Developing Country" screening strategies (usually specified by screening once, twice, or three times in a woman's life), women with lesions covering over 75% of the cervix, extending to the vaginal wall or 2mm beyond the cryotherapy tip, and architectural cervical abnormalities are ineligible. Women deemed ineligible are referred to a secondary facility (e.g., district or regional hospital) for diagnostic testing (e.g., colposcopy/biopsy).
- Successful treatment returns women to normal and women lose their infections.
- Women with detected cancer are not screened. Women with detected cancer are referred to secondary or tertiary hospitals.

Vaccination

- Vaccine effect begins at the specified Vaccine Start Age.
- Vaccine Coverage determines the proportion of the population that receives the vaccine.
- Vaccine Factor, conditional on being vaccinated, determines the probability that the vaccine provokes an immune response.
- Women face a probability of receiving each of three doses, and a woman's possible level of protection depends on the number of doses received (Vaccine Degree). All vaccine doses are administered at the same time, receiving full protection.
- If a woman has had a prior infection before vaccination, her Vaccine Degree, level of type-specific protection, can be reduced.

- Vaccine protection may wane.
- There is no correlation between natural immunity and vaccine immunity.
- Vaccination does not require a first infection for activation, as in natural immunity.
- As Harvard-CC is static, herd Immunity is not currently captured.

Costs

- Cost per vaccinated women includes three doses, wastage, delivery, and programmatic costs. We assume the cost of the vaccine increases linearly with the number of doses. We assume this cost includes health provider time delivering the vaccine, vaccine wastage, disposable supplies, equipment, and facilities as well as patient time and transport.
- Screening costs are categorized costs into direct medical costs (e.g., staff, disposable supplies, equipment, and specimen transport), women's time costs (time spent traveling, waiting, and receiving care), transportation costs, and programmatic costs.
- Costs for diagnosis and treatment, including costs associated with false-positive results, referral of women ineligible for cryosurgery, and treatment complications are included.
- Cancer treatment costs are applied at the time of cancer diagnosis and are incurred by the length of survival.

Cost-effectiveness analyses

- Both costs and benefits (life expectancy) are discounted and can be set to begin at a specified age. Utilities can vary by age and health state (no cancer and cancer state) and screening/diagnostic test results.

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PARAMETER OVERVIEW

SUMMARY

Numerous parameters are required for Harvard-CC; these parameters fall into five general categories: 1) model specifications/population demographics, 2) natural history, 3) cost/benefit, 4) vaccination, and 5) screening.

BACKGROUND

To parameterize the model, we estimate initial plausible ranges for each model input parameter based on data from the published literature (e.g., probabilities relating to disease progression/regression, mortality, test/treatment characteristics, costs). To the extent possible, primary data from the specified country are used.

PARAMETER LISTING OVERVIEW

Parameters of the model can be divided into five general categories.

Model Specification/Population Demographics parameters include: the size of the cohort, the start and end ages for simulated males and females in the model, the age which to begin counting events and costs, the discount rate, and the random number generator seed.

Natural History parameters include:

- All-cause mortality (stratified by age) (Human Mortality Database)
- Cervical cancer mortality (by duration and further adjusted by age) (SEER 9)
- Cervical cancer incidence (Connecticut State Registry historical data for pre-screening era, SEER for incidence in screening era)
- Hysterectomy rates (by age) (Adjusted inpatient National Hospital Discharge Survey (NHDS) data using State Ambulatory Surgery and Services Database (SASD) and validated to BRFFS)
- HPV incidence (by age and by type)
- HPV progression and regression (by duration of infection and by type) cancer symptom detection (by age and by stage)
- Natural immunity factor and degree (by type)

Sexual Mixing/HPV Transmission:

- Sexual activity category (National Survey of Family Growth (NSFG) and NHANES)
- Age of sexual debut (NSFG and NHANES)
- Partnership duration (NSFG)

Screening parameters include:

- Screening algorithm and each algorithm's associated parameters (e.g. interval until next procedure dependent on current result)
- Screening start and stop ages
- Screening frequency/coverage (stratified by percentage of population) (BRFSS for 1988-2007 with adjustment for reporting inflation, New Mexico HPV Pap Registry (NMHPVPR) for 2008-current)
- Superscreening (increased surveillance due to an abnormal screening result)
- Subscreening (reduced screening due to persistent normal screening results),
- Compliance at each screening step, e.g. primary screen, follow-up, colposcopy, or treatment (allowed to be conditional on screening result) (BRFSS, NHIS)
- Screen wait times before each screening step,
- Test characteristics of different procedures:
    - sensitivity of pap - (Athena Trial Koliopoulos et al Gyn Onc 2007)
    - colposcopy/biopsy test performance (NMHPVPR Stoler et al Am J Surg Path 2015)
    - HPV testing alone and cotesting (Arbyn et al 2012 Vaccine)

Vaccination parameters include:

- Vaccine age and coverage
- Vaccine factor
- Vaccine degree (by type and by number of doses)
- Reduction of effect due to prior infection
- Wane start and duration

Cost/Benefit parameters include:

- Quality of life utilities
- Costs:
    - Screening costs for each screening component (screening procedures such as pap or HPV DNA test, colposcopy, treatment; patient time and travel; office visit) (Centers for Medicare & Medicaid Services, 2017 Clinical Diagnostic Laboratory Fee Schedule)
    - Cancer treatment costs by stage (applied upon detection for duration of survival) (Mariotto et al JNCI 2011)
    - Background healthcare costs by age and gender (CMS, National Health Statistics Group)
    - Vaccine cost by dose

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COMPONENT OVERVIEW

SUMMARY

The Harvard-CC is extremely complex. Input parameters must be read in, population-level attributes must be specified, and every month of every woman in the model cohort must be simulated. Afterwards, results must be aggregated and output.

OVERVIEW

The Harvard-CC has four main components, as described below.

COMPONENT LISTING

Model Specification/Population Demographics:

The Harvard HPV Stochastic Model is an empirically-calibrated stochastic first-order Monte Carlo simulation model of cervical cancer. The individual-based state-transition model reflects multiple HPV types, can explore interactions between screening and vaccination, and is able to be linked to a companion transmission model allowing incorporation of herd immunity effects. Key uncertain parameters of the model were calibrated to empirical data using a likelihood-based approach that formally compares how well model outcomes produced by each generated parameter set match multiple calibration targets, such as age- and type-specific HPV prevalence and age-specific incidence of cervical cancer.

Natural History:

Disease progression in the model is characterized as a sequence of monthly transitions between health states. Health states in the model, descriptive of each patient's underlying true health, include infection status, grade of cervical intraepithelial neoplasia (CIN), and stage of cancer. HPV types are categorized as high-risk type 16; high-risk type 18; high-risk type 31; high-risk type 33; high-risk type 45; high-risk type 52; high-risk type 58; other high-risk types, including 35, 39, 51, 56, 59, 66, 68, 73, and 82; and low-risk types, consisting of nononcogenic types of HPV, including 6, 11, 26, 32, 34, 40, 42, 44, 53, 54, 55, 57, 61, 62, 64, 67, 69, 70, 71, 72, 81, 83, and 84. Health states reflecting invasive cancer include both detected and undetected cancer; a cancer is considered detected when either symptoms occur that lead to a correct diagnosis or a previously undiagnosed malignancy is detected by screening.

The time horizon of the analysis incorporates a woman's entire lifetime. Individual women enter the model (usually at age 9), prior to sexual debut, and are simulated one at a time using a series of monthly transitions between health states. The probabilities governing these transitions depend on age; HPV type; duration of HPV infection; type-specific natural immunity; as well as a woman's history of prior infection, previously treated CIN, and patterns of screening. Each month, women can become infected with HPV and those with HPV infection may have cervical histopathologic changes that can be detected by screening or diagnostic procedures. Women with cervical intraepithelial lesions can progress, regress or persist. Women who progress to invasive cancer can become symptomatic or can progress to more advanced stages of cervical cancer. All women are at risk for death from other causes. Women with undetected cancer are additionally subjected to age-based hysterectomy rates. If a woman undergoes a hysterectomy, all HPV-related disease progression stops and are only subject to the risk of death from other causes.

The simulation model is evaluated as a first order Monte Carlo simulation, in which events are simulated for a sequence of individuals using random numbers based on event probabilities (e.g., the probability of a woman with persistent HPV 16 and CIN 3 progressing to invasive cancer), thus producing individual "case histories". This method permits the risk of any event to depend on an individual's history, an important attribute when comparing screening, vaccination, and combined screening and vaccination. The model tracks each woman, one after the other, from entry into the model until death, and maintains a tally of all clinical events and accrued costs throughout her lifetime, as well as composite month-by-month totals. By running large numbers of simulated cases (e.g., 1,000,000), stable estimates of long-term outcomes are produced for each strategy in the form of a distribution of survival values and lifetime costs.

In general, the model simulates single cohort (i.e., "closed"), but may also function as an open population model, simulating multiple cohorts of women to form a cross-section of the population over time. The open population mode incorporates differences due to calendar year of birth to reflect secular changes in cohort risk factors, evolution of screening methods, and changes in life expectancy, among other factors.

Screening:

Screening strategies are differentiated by the modality of screening test, sensitivity and specificity, number of clinical visits, screening frequency, compliance, and targeted ages.

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Vaccination:

Vaccination strategies vary according to age of vaccination, coverage, and assumptions regarding cost, duration of immunity, number of doses received, and magnitude of protection.

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OUTPUT OVERVIEW

SUMMARY

The Harvard CC Model provides health and intervention events, costs, and life years of the simulated population. More detailed and specific outputs can also be generated.

OVERVIEW

The Harvard HPV Stochastic Model simulates a cohort of women one-at-a-time, month-by-month from a designated starting age (usually age 9) until death. During this simulation, the model aggregates and averages various health-related events and costs for the entire cohort. The model also keeps track of health-related events on a month-by-month basis.

OUTPUT LISTING

The Harvard-CC model outputs population-level statistics for the modeled cohort as detailed below.

Population Demographics:

- Number of life years simulated
- Total population (hysterectomized women included and excluded)
- Population life expectancy (discounted and undiscounted, total and quality-adjusted)
- Total hysterectomies

Natural History:

- Number of HPV infections (stratified by type and gender in vaccination analyses)
- Total number of lesions (stratified by CIN2 and CIN3)
- Total number of women with lesions
- True health states of women (i.e., CIN) in addition to the results of screening tests (e.g., cytology test results: "atypical squamous cells of undetermined significance," ASCUS; "favoring high-grade," ACIN23;

"low-grade squamous intraepithelial lesions," LSIL; "high-grade squamous intraepithelial lesions," HSIL)

Screening/Treatment:

- Number of women screened
- Number of screening procedures (e.g. cytologies, HPV tests, colposcopies, treatments)
- Total number of detected and undetected cancers
- Total number of symptoms detected, and screen detected cancers
- Stage at detection
- Total number of detected and undetected cancer deaths
- Total lifetime detected cancer risk and mortality
- Life years gained through screening
- Average colposcopies per woman by age

Vaccination:

- Number of vaccinations

Costs:

- Total cost per person (discounted and undiscounted)

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RESULTS OVERVIEW

SUMMARY

The Cervical-CISNET working group is currently conducting several comparative analyses across modeling sites, including our Screening Base Case analyses and our Vaccination Base Case analyses. Results of these comparative modeling efforts will be detailed here are analyses are finalized and results are published for the broader scientific community.

OVERVIEW

See Output Overview section.

RESULTS LIST

The outputs from the miscellaneous output file can be used to directly compare different policy scenarios.

See Output Overview section.