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UMN Cervical: Model Profile

University of Minnesota

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Version Table

Version	Date	Notes
1.0.00	2025-09-30	Major update
HI.001.03202020.9999	2020-03-20	Historical release

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Readers 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.

Model Purpose

Summary

This document summarizes the overall goal of the University of Minnesota Cervical Cancer model (UMN-HPV CA).

Purpose

The UMN-HPV Cancer (CA) Model was developed to model the natural history of human papillomavirus (HPV) infection and resulting health outcomes related to cervical cancer. UMN-HPV CA simulates different interventions to quantify the effectiveness of HPV vaccination and cervical cancer screening. Model findings are intended to inform public health policies and explain population-level trends in cervical cancer incidence and mortality.

UMN-HPV CA Model consists of two models: a dynamic transmission model and a cohort model. The dynamic transmission model is able to replicate sexual acquisition of type-specific HPV and HPV-induced cervical carcinogenesis. The HPV transmission is simplified in the cohort model and is modeled as an incidence rate. Both models simulate the natural history of HPV infection, cervical pre-cancer and cancer, as well as primary and secondary prevention through vaccination and screening. The UMN-HPV CA Model can be run in two ways 1.) simulation of a single birth cohort 2.) simulation of multiple cohorts reflecting the United States population.

Model Overview

Summary

This document provides an overview of the UMN-HPV CA Model's structure and components.

Purpose

The UMN-HPV CA Model was developed to examine HPV transmission and cervical cancer natural history dynamics and the cost-effectiveness of vaccination and screening strategies. Results from the model are intended to be disseminated broadly to decision-makers and stakeholders to provide evidence and recommendations for cancer prevention and control guidelines. Refer to Model Purpose for detail.

Background

The American Cancer Society estimates that more than 13,000 new cervical cancer cases and 4,000 cervical cancer deaths will occur in 2024. Increasing human papillomavirus (HPV) vaccination coverage and cervical cancer screening uptake are two major interventions targeting populations of different ages who are at risk of cervical cancer. It is important for decision-makers and stakeholders to know the effectiveness of implementing cervical cancer preventive interventions.

The UMN HPV CA model was developed based on the well-understood cervical cancer natural history.

The UMN HPV CA Model contains:

1. A natural history component that tracks progression and regression between HPV infection, precancer states, and cancer states stratified by different HPV types.
2. A vaccination component that allows for a reduction in the likelihood of HPV infections and captures herd immunity benefits;
3. A screening and treatment component that allows for the detection and removal of precancerous lesions and diagnosis of preclinical cervical cancers; and
4. A detection and survivor component for all women diagnosed with cervical cancer.

The UMN HPV CA Model specifically incorporates:

1. Population-level sexual behavior trends by age and sex.
2. Population-level trends in vaccination rates and vaccine efficacy.
3. Population-level trends in competing risks for cervical cancer, namely hysterectomy and background mortality;
4. Population-level trends in cervical cancer screening participation rates and test performance of various screening options to detect precancerous and cancerous lesions.

The primary model outcomes are HPV prevalence, cervical cancer incidence, and cervical cancer deaths. These outcomes are compared to country and state-level cancer registry data, incidence data from the Surveillance, Epidemiology, and End Results (SEER), and mortality data from the US Vital Statistics. Additional outcomes include number of life years and quality-adjusted life years (QALY's) gained under various screening and vaccination strategies as compared to natural history.

Model Description

The natural history of HPV infection and cervical is a state-transition micro-simulation model that simulates women who are at average risk (defined as not immune-compromised and not HPV vaccinated). The transitions are age dependent. The cycle length is 1 year. The cohort starts at age 9 and all girls are assumed to

be normal (i.e., not HPV infected). Every year, women are at risk of becoming infected with HPV stratified by type (described later). Women who are infected can clear their infection, stay infected or progress to CIN (either CIN 1 or directly to CIN 2/3). Women with CIN 1 can progress to CIN 2 or CIN 3 and/or regress (to normal or HPV). Women with CIN 2 can remain in the same state, progress to CIN 3, or regress (to CIN 1, HPV or normal). Women with CIN 3 can remain in the same state, progress to cancer (Stage I), or regress (to either CIN or normal). Cancer is modeled as 4 stages (Stage I, Stage II, Stage III and Stage IV). The state-transition diagram of the natural history of HPV infection and cervical cancer stratified by age and HPV type is shown in Figure 1.

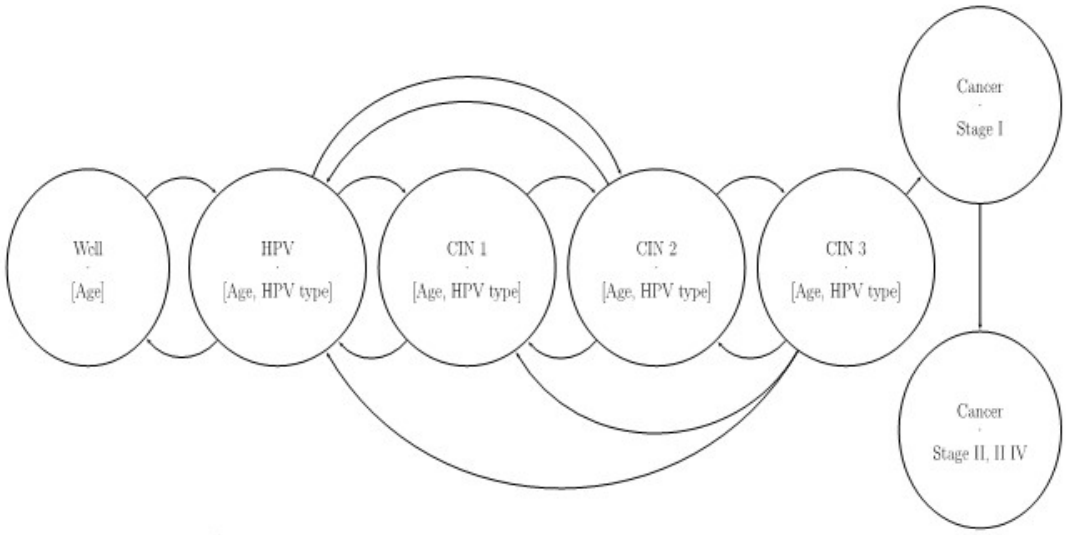

Figure 1. State-transition diagram of the natural history of HPV infection and cervical.

Assumption Overview

Summary

This section outlines the UMN-HPV CA model assumptions.

Background

The UMN-HPV CA model relies on assumptions regarding aspects of the disease's natural history prior to diagnosis, screening effectiveness and outcomes, vaccination efficacy, and the costs and harms resulting from different prevention strategies.

Assumption Listing

Population demographics

Both the cohort and dynamic models assume birth and mortality rates consistent with U.S. census data available in the Human Mortality Database (formerly Berkeley Lifetables). These rates are annual based on 2015 cohort life tables.

Sexual behavior

We used National Survey for Family Growth (NSFG) data from 2010-2011 to assign sex- and age-specific distributions of the maximum number of heterosexual partners possible in a given year. Sexual mixing is assumed to be dependent on an individual's age and maximum number of partners. We assume that concurrent partnerships are possible.
Sexual partnerships were assigned a duration according to sex- and age-specific NSFG data. Individuals that age into a new age group may be reassigned a maximum number of partners and partnership duration. Type-specific sexual transmission of HPV is possible between either gender. We assume all individuals without any immunity in the model are susceptible to HPV infection upon sexual debut, which is age specific.

Natural history of HPV infection

Natural immunity following HPV infection is assumed to provide a varying degree of protection for a lifetime. Natural immunity only occurs in females and is type-specific. We categorized HPV type into four groups based on genotypes: 1.) HPV16 2.) HPV18 3.) High-5 (other pentavalent vaccine types - 31, 33, 45, 52, 58) and 4.) other high-risk (all other HPV types not covered by the nonavalent vaccine - 35, 39, 51, 56, 59, 66, 68). We assumed that co-infection with multiple HPV types is possible. HPV infection can occur at any state in the model among individuals who are sexually active. Transmission is modeled as an annual probability per partnership.

Natural history of pre-cancer

HPV infection may progress to precancer, represented in the model as cervical intraepithelial neoplasia stages 1, 2, and 3, with direct progression allowed to any of the three CIN states. Limited empirical evidence exists to inform rates of progression and regression between precancer stages. Therefore, estimates of natural history regression and progression have been calibrated according to HPV prevalence and cancer incidence targets, and transitions depend on age and HPV type. Each year there is a greater probability that the disease will progress to the next proximal stage or regress to the previous stage, but progression and regression may also skip stages. Annual probabilities of total hysterectomies are based on hysterectomy rates in the US in 2009 for ages (15–99) from the National Hospital Discharge Survey (NHDS). Hysterectomy and background mortality are modeled as competing risks.

Natural history of cancer and associated mortality

UMN-HPV CA models adenocarcinoma (ADC) and squamous cell carcinoma (SCC) as combined cervical cancer. Cancer stages are modeled as Stage 1, 2, 3, and 4, according to the International Federation of Gynecology and Obstetrics (FIGO) staging. Women may progress from CIN3 to Stage 1 cancer. Symptomatic

cancers can result in cancer-related mortality. The probability of expressing symptoms is dependent upon the cancer stage. We assume that cancer survivors are no longer at risk of cancer recurrence.

Screening behavior and performance

Screening algorithms are implemented in accordance with the 2019 American Society for Colposcopy and Cervical Pathology (ASCCP) Updated Consensus Guidelines for Managing Abnormal Cervical Cancer Screening Tests and Cancer Precursors. This algorithm recommends a series of primary, triage, and surveillance tests according to prior test results and outcomes. These strategies include cytology, HPV genotyping test, and co-testing, with each test(s) absolute and relative performance modeled in the algorithm. Colposcopy and biopsy can have variable sensitivity and specificity although the base case usually assumes 100% test accuracy. All lesions detected through screening are assumed to be treated although this assumption can be varied.

Vaccination

We assume perfect vaccine efficacy and lifetime vaccine acquired-immunity against vaccine-preventable HPV types in the base case analysis. In secondary analyses, we assume that vaccine failure is possible. Full protection is assumed for a variable duration of time (if no primary failure), after which immunity waves. Both women and men aged 11 to 26 years may be vaccinated in the model in accordance with vaccination guidelines. The vaccination series is modeled based on current guidelines but can be administered at varying intervals.

Costs and harms

Each step in screening, (pre)cancer and cancer diagnosis and treatment can have an associated disutility and cost. These are based on the literature and are detailed in elsewhere.

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Parameter Overview

Summary

This section describes the key parameters of the UMN-HPV CA Model.

Background

This model is informed by data sources common to the CISNET modeling group.

Transition probabilities

We model the transition probabilities from four different health states of the natural history model of HPV infection and cervical cancer: HPV, CIN1, CIN2, CIN3. The transition probability is a function of age and HPV type.

Parameter Listing Overview

Parameter Listing	Relevant assumptions	Data Source
Population parameters		
Population size	Variable	-
Population distribution	We assume a female population for cohort model; the sex ratio at birth is used to estimate the female-to-male ratio of newborns in the population (0.51)	Human Mortality Database, formerly Berkeley Lifetables (1995).
Background mortality	Annual probability of death (age, yearly, by gender)	Human Mortality Database, formerly Berkeley Lifetables (1995).
Disease transmission parameters		
Birth rate	Annual birth rate (age, yearly, by gender)	Human Mortality Database, formerly Berkeley Lifetables (1995).
Age distribution of population	Assumed distribution of population at model initiation by age and gender given by lifetables	Human Mortality Database, formerly Berkeley Lifetables (1995).
Sexual activity	(5-year age groups, based on NSFG gender-specific distributions of number of partners in the last 12 months). Partnerships may be concurrent.	CDC. National Survey of Family Growth. 2010-2011.
Partner age	Distribution of partner age	CDC. National Survey of Family Growth. 2010-2011.
Partnership duration	Maximum number of years a partnership can last	CDC. National Survey of Family Growth. 2010-2011.
Initial infection (cohort model)	(by HPV type)	Calibrated
HPV transmission	Gender-specific annual probability of contracting HPV per infected partner	Calibrated
HPV type	Distribution of HPV type (16, 18, HI-5, other high-risk) condition on infection	Han JJ, Beltran TH, Song JW, Klaric J, Choi YS. Prevalence of genital human papillomavirus infection and human papillomavirus vaccination rates among US adult men: National Health and Nutrition Examination Survey (NHANES) 2013-2014. JAMA Oncol. 2017;3(6):810-816. doi:10.1001/jamaoncol.2016.6192.
HPV clearance	Annual probability of clearing HPV infected	Calibrated
Natural History parameters		

Parameter Listing	Relevant assumptions	Data Source
Competing risk of hysterectomy	New denominator at younger ages corrected for screening coverage	NHDS (2009) and US Census data (2009), (BRFSS)
Infection progression / regression for normal – CIN3 states	By HPV type and age	Calibrated
Transition probabilities for cancer states	Assumed to be constant for all types	Calibrated
Cancer symptom detection	Assumed to be constant for all types	Informed by Myers, E., McCrory, D., Nanda, K., Bastian, L., & Matchar, D. (n.d.). Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. American Journal of Epidemiology., 151(12), 1158-1171.
Cancer survival	Currently modeled as constant across ages (5-year probability at time of detection given years of survival)	SEER 9, year of diagnosis = 1975+
Targets		
HPV Prevalence	Used linear interpolation to generate yearly targets. (age, and type-specific)	Wheeler CM, Ph D, Hunt WC, et al. A Population-based Study of HPV Genotype Prevalence in the United States: Baseline Measures Prior to Mass HPV Vaccination. 2014;132(1):1-19. doi:10.1002/ijc.27608.A. Additional age ranges per personal correspondence
Cancer Incidence	These values were generated by fitting a line just above the incidence curves from IARC CI5C, 1959-1963, CTR, 1950-1954, and CTR, 1955-1959, and by applying type-specific % from Mona Saraiya, personal communications (see HPV Type Distribution in Cancer)	IARC CI5C, 1959-1963, CTR, 1950-1954, and CTR, 1955-1959. Mona Saraiya, personal communications. Data received 10/03/2016 via email
HPV Type Distribution in Cancer	Total cervical cancer (ADC +SCC), conditioned on HPV+ status	Mona Saraiya, personal communications. Data received 10/03/2016 via email
CIN Prevalence	CIN curves generated by review of recent literature and clinical trials	**1.** Goldie SJ, Grima D, Kohli M, Wright TC, Weinstein M, Franco E. A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. Int J Cancer. 2003;106(6):896-904. doi:10.1002/ijc.11334. **2.** Hariri S, Johnson ML, Bennett NM, et al. Population-based trends in high-grade cervical lesions in the early human papillomavirus vaccine era in the United States. Cancer. 2015;121(16):2775-2781. doi:10.1002/cncr.29266. **3.** Joura EA, Ault KA, Bosch FX, et al. Attribution of 12 high-risk human papillomavirus genotypes to infection and cervical disease. Cancer Epidemiol Biomarkers Prev. 2014;23(10):1997-2008. doi:10.1158/1055-9965.EPI-14-0410. **4.** Kitchener HC, Canfell K, Gilham C, et al. The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: Extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. Health Technol Assess (Rockv). 2014;18(23):1-195. doi:10.3310/hta18230. **5.** Peto J, Gilham C, Deacon J, et al. Cervical HPV infection and neoplasia in a large population-based prospective study: the Manchester cohort. Br J Cancer. 2004;91(5):942-953. doi:10.1038/sj.bjc.6602049. **6.** Ramanakumar A V, Naud P, Roteli-Martins CM, et al. Incidence and duration of type-

Parameter Listing	Relevant assumptions	Data Source
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HPV Type Distribution in CIN	-	Joste NE, Ronnett BM, Hunt WC, Pearse A, Langsfeld E, Leete T, Jaramillo M, Stoler MH, Castle PE, and Wheeler CM. New Mexico HPV Pap Registry Steering Committee. Cancer Epidemiol Biomarkers Prev January 1 2015 (24) (1) 230-240;DOI: 10.1158/1055-9965.EPI-14-0775, NMHPVPR
Vaccination parameters		
Vaccine efficacy	Vaccine failure possible. Full protection assumed at 100% efficacy and lifetime duration for vaccine-preventable HPV types in base case analysis.	-
Natural immunity	Full protection assumed for lifetime. Natural immunity is assumed to occur in females only.	-
Vaccination parameters		
Cytology test performance	Pooled absolute sensitivity and specificity	Koliopoulos, George et al. Diagnostic accuracy of human papillomavirus testing in primary cervical screening: A systematic review and meta-analysis of non-randomized studies. Gynecologic Oncology. January 2007 (104) (1) 232-246
HPV and Cotest test performance	Relative sensitivity and specificity	Arbyn M, Ronco G, Anttila A, Meijer C, Poljak M, Ogilvie G, Koliopoulos G, Naucler P, Sankaranarayanan R and Peto J. Evidence Regarding Human Papillomavirus Testing in Secondary Prevention of Cervical Cancer. Vaccine, November 20 2012 (30) F88-F99. ATHENA Summary of cobas HPV Test Result and Central Pathology Review Panel Diagnosis in the Primary Screening Population (>=25 years) at Baseline
Screening practice	% of women who screen at different intervals (Q1-Q5)	Cuzick J, Myers O, Hunt W C, Saslow D, Castle, PE, Kinney W, Waxman A, Robertson M, Wheeler CM. and on behalf of the New Mexico HPV Pap Registry Steering Committee (2015), Human papillomavirus testing 2007–2012: Co-testing and triage utilization and impact on subsequent clinical management. Int. J. Cancer, 136: 2854–2863. doi:10.1002/ijc.29337; NMHPVPR - sent by Curtis Hunt on 1/17/2013

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Component Overview

Summary

This document outlines the components that make up the UMN-HPV CA Model.

Overview

The model is made up of the following components: (1) an HPV transmission component that simulates the heterosexual HPV transmission, (2) a cervical carcinogenesis component that simulates the progression of HPV infection to cervical cancer, (3) a vaccination component that simulates the protective effect of the HPV vaccine, (4) a screening, diagnosis and treatment component that simulates early detection and treatment of precancerous lesion and cancer, and (5) a cancer treatment and survival component that simulate survival of clinically detected cancers.

Component Listing

HPV transmission

Transmission of HPV infections in males and females is modeled in the dynamic individual-based model, with individual partnerships characterized by sex, age, and duration. Females and males form heterosexual partnerships as they age, and transmission of type-specific HPV can occur as a function prevalence of HPV in the population and female-to-male or male-to-female transmission probabilities of HPV per susceptible-infected partnership. Following clearance of HPV, female individuals may develop natural immunity, reducing future risk of that same type of infection. Women with high-risk infection can develop precancerous lesions (i.e., cervical intraepithelial neoplasia (CIN1, CIN2 or CIN 3), which may regress naturally, and those with CIN 3 may develop invasive cancer. Death can occur from age- and sex-specific background mortality or excess mortality in women with invasive cervical cancer.

Cervical carcinogenesis

Both the dynamic and cohort models include health states that reflect cervical carcinogenesis associated with HPV-16, 18 and other high-risk HPV types. In these models, women transition between health states, which reflect the individual's underlying true health and include HPV infection status, grade of CIN (CIN 1, CIN 2 and CIN 3), and stage of invasive cancer (I through IV). In the cohort model, women enter the model before sexual debut and transition between health states according to probabilities that depend on age, HPV type, type-specific natural immunity, CIN status, and treatment history. Death can occur each year from non-cervical cancer causes from all health states, or from cervical cancer after its onset. Hysterectomy is modeled as a competing risk.

Vaccination

The dynamic model is used to project the effects of HPV vaccination in reducing HPV-16, HPV-18 and other vaccine-preventable high-risk type infections over time, capturing both direct and indirect benefits. The dynamic model can also account for the impact of these effects on CIN and cancer. The immunity conferred by vaccination has full protection of a lifetime. The model can account for vaccine inefficacy.

Screening, diagnosis and treatment of CIN

Both models can accommodate detailed features of screening strategies, including algorithms that are based on a single test or multiple tests (either in parallel or serial). The models reflect screening, follow-up, and treatment recommendations based on American Cancer Society (ACS), US Preventive Services Task Force (USPSTF) and American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, but assumptions can be modified flexibly. The models both incorporate a detailed post-treatment surveillance component. (3)

Cancer treatment and survival

The models include cancer states by stage (I through IV) and conditional probabilities of survival based on stage of detection. The models also include a separate state for survivors and cancer-related deaths based on data from the Surveillance, Epidemiology, and End Results (SEER) Program.

Output Overview

Summary

This is a general overview of the outputs generated by the UMN-HPV CA model.

Overview

Base Case Outputs

Base Case outputs assume that no screening is performed, and the model is calibrated to yearly HPV prevalence, cancer incidence, and CIN1, CIN2, and CIN3 targets. The following outputs are generated and aggregated in five-year age groups for comparison to other CISNET models:

1. HPV prevalence by age and HPV genotype
2. HPV type distribution in cancer by age
3. Prevalent preclinical (undetected) cancer by age, cancer stage and HPV genotype
4. Prevalent clinical (detected) cancer by age and cancer stage
5. Clinical cancer stage distribution (proportion) by age
6. Clinical cancer incidence per 100,000 by stage and age or overall clinical cancer incidence
7. HPV-type distribution in CIN1, 2, and 3
8. CIN 1, 2, and 3 prevalence
9. Cancer mortality per 100,000

Cervical Cancer Screening Outputs

Screening outputs after overlaying screening on natural history are generated. Screening outputs were generated from various screening strategies with different primary screening tests and triage methods. The following outputs were generated and aggregated in five-year age groups for comparison to other CISNET models:

1. Average Screening tests per woman by age groups
2. Average Pre-cancer treatments per woman by age groups
3. Average colposcopies per woman by age groups
4. Average false-positive test results per women by age groups
5. Life years gained through screening

Output Listing

Cohort Model Base Case Outputs	
Note: these outputs also produced when initial screening carried out	
Total population alive: Hysterectomized women included and excluded	Counts by age, year, and hysterectomy status
HPV Prevalence:	Counts by age, year, and HPV type (four groups: HPV16, HPV18, High 5 HPV types, all other high-risk HPV)
Prevalent (undetected) Cancer Cases	Counts by age, year, and cancer stage
Prevalent Clinical Cancer Cases	Counts by age, year and cancer stage
Incident Clinical Cancer Cases by type	Counts by age, year and HPV type
Incident Clinical Cancer Cases by stage	Counts by age, year and cancer stage
Total Cancer Rate per 100,000 women	Counts by age and year
Clinically Detected Cancer Deaths	Counts by age and year
Cancer Death per 100,000 women	Counts by age and year
Prevalent Counts of CIN 1	Counts by age, year, and HPV type
Prevalent Counts of CIN 2	Counts by age, year, and HPV type
Prevalent Counts of CIN 3	Counts by age, year, and HPV type

Screening Outputs	
Average Screening tests per woman by age groups	Counts by age, year and screening strategy
Average Pre-cancer treatments per woman by age groups	Counts by age, year and screening strategy
Average colposcopies per woman by age groups	Counts by age, year and screening strategy
Life years gained through screening	Total life years per strategy (no screening, Q1-Q5)
Quality adjusted life years	Total quality-adjusted life years per strategy
Outcomes for cervical cancer screening strategies over the lifetime of screening (screening end age 65)	
Number of Cytology tests performed	Total number of cytology tests administered in a cohort from ages 20-100, irrespective of primary, triage, or surveillance context
Number of HPV tests performed	Total number of HPV genetic tests administered in a cohort from ages 20-100, irrespective of primary, triage, or surveillance context
Number of Total tests performed	Total number of tests administered in a cohort from ages 20-100, irrespective of primary, triage, or surveillance context
Total number of Colposcopies performed	-
Total number of CIN2, CIN3 lesions detected through screening	-
Total number of CIN3 lesions and cervical cancers detected through screening	Excludes symptomatic cancers diagnosed clinically
False positive colposcopies	Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection
Total number of cervical cancer cases per 100,000	-
Total number of deaths due to cervical cancer per 100,000	-

Results Overview

Summary

This document outlines the results that the UMN-HPV CA Model generates.

Results List

Expanding upon US Preventive Services Task Force Decision Analysis Screening Outputs

CISNET teams carried out the full screening algorithm to expand upon Harvard's analysis of the U.S. Preventive Services Task Force Decision Analysis of primary HPV testing by 1) adding costs, 2) including screening adherence, 3) reflecting obstetric harms from pre-cancer excisional treatment. UMN-HPV CA provides comparative results for this analysis carried out by the Harvard CISNET group. This analysis was composed of 19 screening strategies including cytology, HPV primary testing, cotesting, and combinations of these tests in accordance with the algorithm. Outcomes were calculated from age 21 to 100 years. A series of sensitivity analyses will be carried out by varying the triage methods, screening interval, and adherence to recommendations. The following results were compared per 1,000 women:

1. Number of cytology tests
2. Number of HPV tests
3. Total number of tests, irrespective of primary, triage, or surveillance context
4. Number of colposcopies
5. Number of CIN2 and CIN3 lesions detected
6. Number of CIN3 lesions or higher detected (not including those detected by clinical symptoms)
7. Number of false positives, defined as the total colposcopies that did not result in CIN2, CIN3 or cancer detection
8. Number of cervical cancer cases
9. Number of deaths due to cervical cancer
10. Number of life-years

Key References

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