Supplement to: Identifying strategies to accelerate the elimination of cervical cancer in British Columbia: a modelling study

Reka E. Pataky, PhD[1,2], Sara Izadi-Najafabadi, PhD[1,2], Laurie W. Smith, MPH BN[1,3], Anna Gottschlich, PhD[4], Diana Ionescu, MD[5,6], Lily Proctor, MD MPH[5,6], Gina S. Ogilvie, MD DrPH[3,7*] and Stuart Peacock, DPhil[1,8*]

1. Cancer Control Research, BC Cancer, Vancouver BC
2. Canadian Centre for Applied Research in Cancer Control (ARCC)
3. Women's Health Research Institute, BC Women's Hospital and Health Centre, Vancouver BC
4. Karmanos Cancer Institute, Wayne State University, Detroit MI, USA
5. Faculty of Medicine, University of British Columbia, Vancouver BC
6. Cervix Screening Program, BC Cancer, Vancouver BC
7. School of Population and Public Health, University of British Columbia, Vancouver BC
8. Faculty of Health Sciences, Simon Fraser University, Vancouver BC

*co-senior authors

1. OncoSim-Cervical model: vaccination and screening design

The OncoSim model, previously called the Cancer Risk Management Model (CRMM in earlier publications), is led and supported by the Canadian Partnership Against Cancer (CPAC), and developed by a team from Statistics Canada [1]. There are currently five OncoSim models: four cancer-specific models for breast, colorectal, lung and cervical cancer, and a fifth "all cancers" model for high-level projections of cancers across 32 anatomic sites [2].

An interacting-agent microsimulation model of HPV transmission and infection (HPVMM; previously called CRMM-HPV in Miller *et al.*) is integrated with OncoSim-Cervical, a microsimulation model that simulates the natural history of cervical cancer in the Canadian population[3].

HPVMM simulates HPV transmission through sexual interactions based on age- and sex-dependent patterns of heterosexual partnership. The transmission and natural history of HPV infection and clearance is modeled separately for HPV type 16, 18, 11, 6, other high-risk types, and other low-risk types. Model parameters were calibrated to fit HPV prevalence by age and HPV type from published data [4, 5] and unpublished data from the HPV FOCAL trial [6]. Figures illustrating model fit are available in Miller *et al.*[3]. HPVMM also models the impact of HPV vaccination programs with parameters for vaccine type (bivalent, quadrivalent, nonavalent), age to vaccinate, sex, vaccine effectiveness, and duration of immunity. Vaccination is modelled as a single state (i.e., vaccinated or unvaccinated). The model does not consider the number of vaccine doses required, and does not model the effect of incomplete courses. In this analysis, we made no changes to the model default assumptions that vaccination is fully effective at stopping transmission of the HPV strains targeted by each vaccine type, and that immunity does not wane over time; however, these parameters can be altered in HPVMM. Herd immunity is not specifically modelled, but can arise in the interacting-agent model as a result of modelled vaccine coverage and protection.

In this analysis, we replicated British Columbia's (BC) historical vaccination program design for all scenarios. Publicly-funded school-based vaccination of girls in Grade 6 (11-12 years old) was launched in 2008 using the quadrivalent HPV vaccine. In 2017, the program was expanded to boys in Grade 6, and the quadrivalent vaccine was replaced with the nonavalent vaccine. Vaccination coverage among girls by Grade 9 was approximately 70% in 2020[7].

Detailed HPV infection rates from HPVMM are input into the OncoSim-Cervical model, to initiate HPV infection in simulated individuals. OncoSim-Cervical then simulates the subsequent incidence of precancerous lesions and progression to cervical cancer through a series of clinical phases. Infection with high-risk HPV is a required to progress through clinical phases. In the absence of screening, clinical detection of cancer is assumed to occur two years after pre-cancerous lesions reach a cancerous state. General model structure and assumptions were adapted from the HPV-Advise model by Brisson *et al.*[8], and calibrated to fit data from the Canadian Cancer Registry[9] and FOCAL trial [6]. For this analysis, we compared simulated cervical cancer incidence rates for BC against historical incidence rates published by the BC Cancer Registry to verify adequate fit (Figure S1).

Screening, follow-up, treatment of precancerous lesions, and cervical cancer treatment have been built into OncoSim-Cervical. Women are recruited into screening based on a user-defined set of parameters defining eligibility, including age, calendar year, and screening history. Screening can be conducted by

different modalities (e.g., cytology or HPV testing), at user-specified time intervals. Individuals enter screening for the first time based on the user-defined recruitment rate. By default, and in this analysis, individuals who do not enter screening on their first attempt do not return to screening. This assumption can be modified in the model. Women who are eligible to be rescreened at the defined screening interval receive a screening test with a probability based on the user-defined rescreening rate. Those who are not rescreened (i.e., who miss a screen) return at their next scheduled screen for another rescreening attempt.

In this analysis, we transitioned from cytology screening to HPV-based screening gradually over 5 years. In the first year, 20% of individuals due for screening were offered primary HPV testing, and the remaining 80% were offered cytology. This was increased in 20% increments each year, until all screen-eligible females were offered HPV testing only.

In OncoSim-Cervical, the results of cytology screening vary according to the underlying disease status of the simulated individual. The distribution of test results is based on the results of Blanks and Kelly[10] and adjusted as part of the calibration process. Results of HPV DNA testing are based on the underlying infection status of the simulated individual, and the test is assumed to be fully accurate (100% sensitivity and 100% specificity for infection status).

Positive results on screening initiate a user-defined follow-up protocol. If an individual is non-compliant with a recommended follow-up, based on the probability defined by protocol-specific follow-up compliance parameters, they are discharged to the regular screening program and return at their next scheduled screening interval.

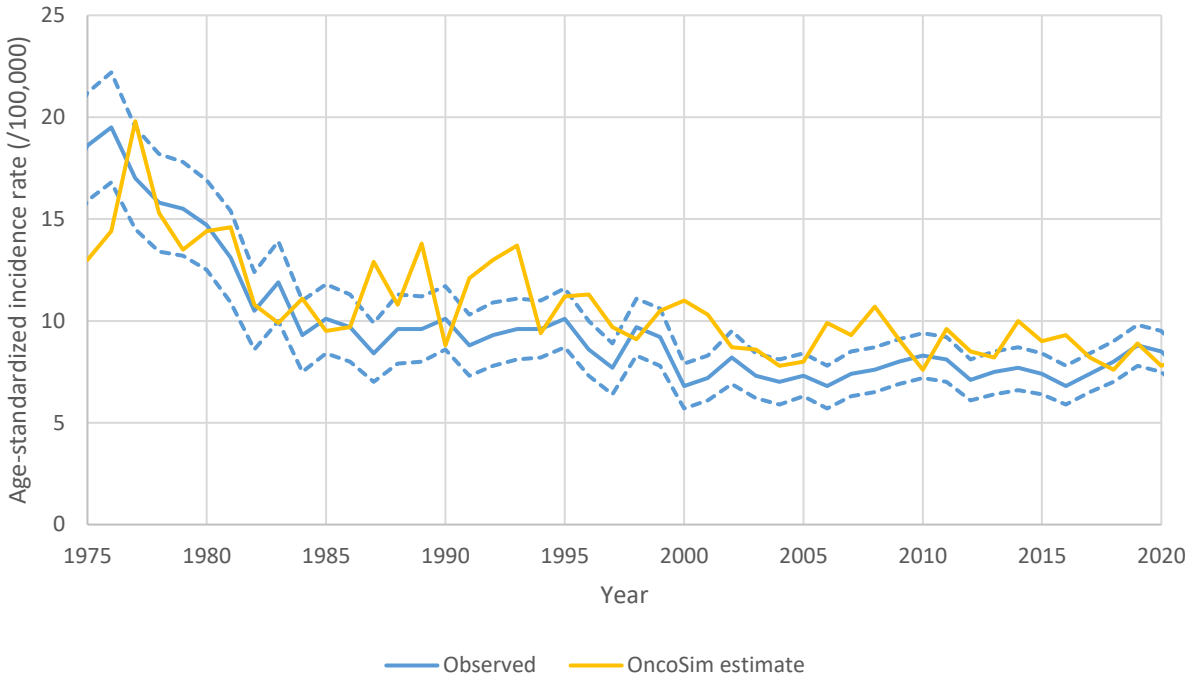

FIGURE S1: HISTORICAL AGE-STANDARDIZED INCIDENCE RATE OF CERVICAL CANCER FOR BRITISH COLUMBIA, 1975-2020

Age-standardized incidence rate of cervical cancer for BC. Dotted lines indicate 95% confidence interval for observed incidence rates. Age standardized to 2011 Canadian Population. Observed value for BC obtained from BC Cancer Registry published estimates [11].

2. Sensitivity Analysis

TABLE S1: SUMMARY OF MODEL PARAMETERS FOR SENSITIVITY ANALYSIS SCENARIOS

Scenario	OncoSim model parameter		
	Immunization coverage	**Recruitment rate (ever screened)**	**Rescreen rate among screened**
Base case	70%	90%	80%
Low participation	70%	**85%**	**75%**
Low vaccination	**65%**	90%	80%
Low participation and low vaccination	**65%**	**85%**	**75%**

The low participation scenario assumes 65% on-time screening, based on the range observed across BC Health Authorities[12]. This is achieved with reduced screening recruitment rate and reduced rescreen rate among screening participants, based on the lower range of historical retention rates[12].

The lower vaccination scenario assumes 65% vaccine coverage, based on the historical range observed in the BC school-based vaccination programs[7].

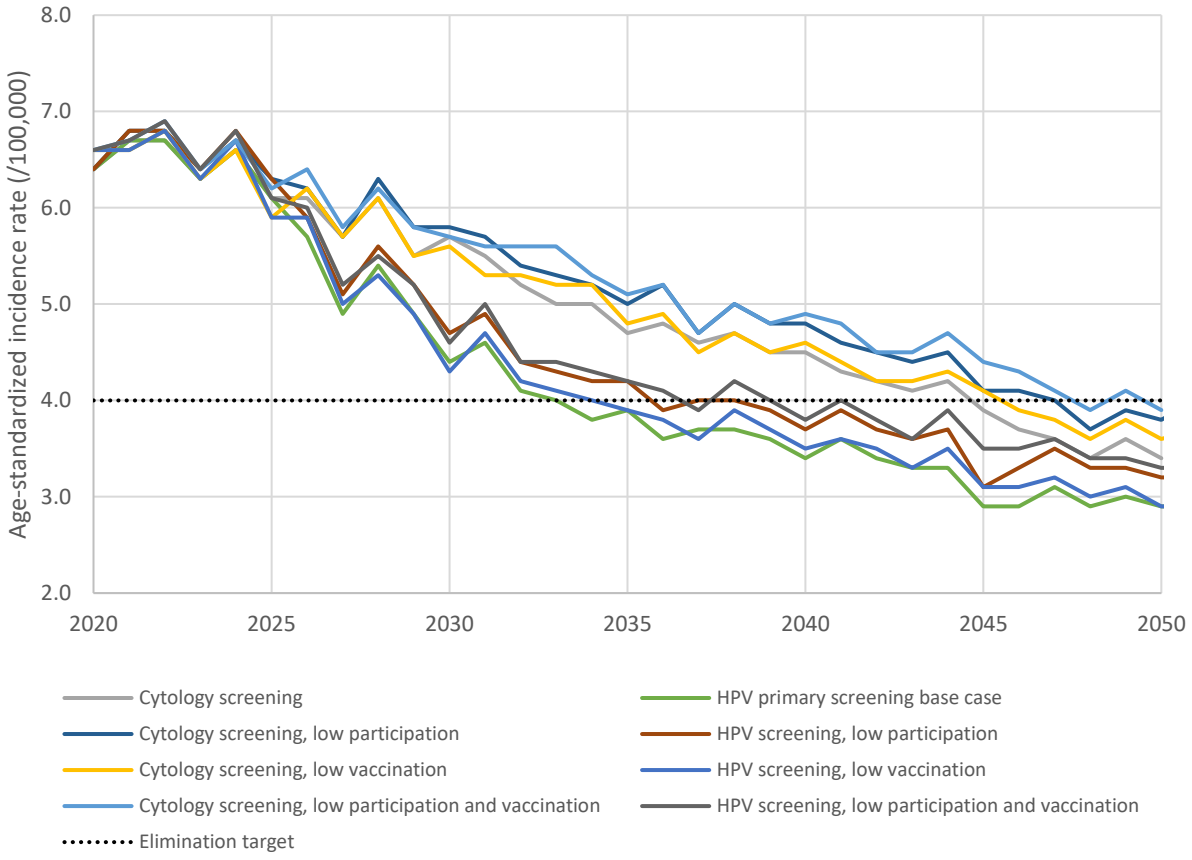

FIGURE S2: PROJECTED AGE-STANDARDIZED INCIDENCE RATE FOR BRITISH COLUMBIA

Age-standardized to WHO World Population [13].

TABLE S2: YEAR OF ELIMINATION OF CERVICAL CANCER, AND NUMBER OF CERVICAL CANCER CASES IN BC, 2023-2050

Scenario	Elimination year	Cervical cancer cases
Cytology screening, base case	2045	6,627
Cytology screening, lower participation	2048	6,945
Cytology screening, lower vaccination	2046	6,699
Cytology screening, lower participation and vaccination	>2050	7,018
HPV screening, base case	2034	5,685
HPV screening, lower participation	2039	6,027
HPV screening, lower vaccination	2035	5,751
HPV screening, lower participation and vaccination	2042	6,102

Elimination defined as age-standardized incidence rate <4.0/100,000, age-standardized to WHO World Population [13]

3. HPV-FRAME Reporting Standards

a) Inputs	Reported? (Y/N)	Reported by age? (Y/N)	Comments*
Target population for intervention	Y	Y	Screening in females age 25-69 years; HPV immunization in 12-year-old females and males
Sexual behaviour	N	Not reported	No change to HPVMM default; details available from CPAC
Cohort examined for evaluation/time horizon	Y	N	Full population of females in BC (dynamic cohort), to 2050. Population counts by age and year available from authors
Quality of life assumptions	Not applicable	Not applicable	Available in OncoSim but not included in this analysis; details available from CPAC
Calibration	Not applicable	Not reported	Model calibration conducted by Statistics Canada and CPAC, using data from Canadian Cancer Registry and FOCAL trial
Validation	Y	N	Graphical comparison of model estimates compared to historical age-standardized incidence rates for cervical cancer from BC Cancer Registry; other model validation conducted by Statistics Canada and CPAC
Costs	Not applicable	Not applicable	Available in OncoSim but not included in this analysis; details available from CPAC
Routine screening behaviour	Y	N	Organized screening. Cytology screening scenario based on BC program design: screening every 3 years, ages 25-69 years. HPV scenarios use partial genotyping (HPV16/18, or other high-risk), every 5 years, ages 25-69 years. Screening parameter definitions and values in Box1, Table 1. Additional information in section 1 of supplement.
Screening test and colposcopy accuracy	N	Not reported	No change to OncoSim default; details available from CPAC.
Abnormal test management	Y	N	Reflex cytology following positive HPV test. Follow-up pathway illustrated in Figure 1.
Diagnostic follow-up of abnormal test	Y	N	Referral to colposcopy for HPV16/18, or other high-risk HPV with abnormal cytology. Follow-up pathway illustrated in Figure 1.
Management by disease grade	N	N	No change to OncoSim default; details available from CPAC.
Sources of information for screening structure and parameters	Y	N	Current program design (cytology); BC HPV self-collection pilot program design. Reports on school-based HPV vaccination from BC Centre for Disease Control. Reports on cervical cancer screening participation from BC Cancer.
b) Outputs	**Reported? (Y/N)**	**Reported by age? (Y/N)**	**Report as calibration or validation target? (Y/N)**
Cancer incidence	Y	N	N. Incidence by age available from authors
Cancer mortality, life-years, quality-adjusted life-years	N	Not applicable	Available in OncoSim but not included in this analysis; details available from CPAC

HPV prevalence, pre-intervention	N	Not reported	Available in OncoSim but not included in this analysis; details available from CPAC
CIN2 detected	N	Not reported	Available in OncoSim but not reported in this analysis; details available from CPAC
Sensitivity analysis on key inputs	Y	N	N. Cancer incidence by age from sensitivity analysis available from authors
Incremental cost-effectiveness	N	Not applicable	Available in OncoSim but not included in this analysis; details available from CPAC

*HPV-FRAME core reporting standards and standards for models of cervical screening [14]

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