Age at last screening and remaining lifetime risk of cervical cancer in older, unvaccinated women: a modelling study

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Summary

Background There is a paucity of empirical evidence to inform the age at which to stop cervical cancer screening. The recommended age to stop screening generally varies between age 50–70 years worldwide. However, cervical cancer incidence and mortality remain high in older women. We used a Markov model of cervical cancer screening to estimate the remaining lifetime risk of cervical cancer at different ages and with different exit screening tests, with the aim of informing recommendations of the age at which to stop cervical cancer screening in developed countries.

Methods For this modelling study, we developed a state transition (Markov) model of cervical cancer natural history and screening. We developed, calibrated, and validated our model using Canadian provincial registries and survey data. To simulate an age-structured population in the model, a new cohort of 236 564 women (one fifth of the population of Canadian women aged 20–24 years in 2012) entered the model every year and were successively modelled in parallel. Successive cohorts entered the model at age 10 years, creating an age-structured population of women aged 10–100 years. Women who had a total hysterectomy were excluded from the analyses. We calibrated our model to human papillomavirus (HPV) infection and cancer incidence with data from Statistics Canada, which compiles the data from 13 individual provincial registries. We chose a three-stage progressive cervical intraepithelial neoplasia model to include differences in management and treatment decisions depending on lesion severity. We modelled infections with four high-risk HPV groups: HPV16 and HPV18; HPV31, HPV33, HPV45, HPV52, and HPV58; HPV35, HPV39, HPV51, HPV56, HPV59, HPV66, and HPV68; and a generic group of other potentially oncogenic HPVs. We estimated 5-year, 10-year, and remaining lifetime risk of cervical cancer for older, unvaccinated women who stopped screening at different ages and underwent different screening tests.

Findings Cervical cancer incidence excluding women with hysterectomies underestimated the incidence of cervical cancer in women with a cervix by up to 71% in women aged 80–84 years. Our model predicted that women without HPV vaccination who have been never screened have a 1 in 45 (95% percentile interval 1 in 32 to 1 in 64) lifetime risk of cervical cancer. Perfect adherence (100% of women screened) to cytology screening every 3 years between the ages of 25 years and 69 years could reduce the lifetime risk of cervical cancer to 1 in 532 women (95% percentile interval 1 in 375 to 1 in 820) without HPV vaccination. Increasing the age at which women stopped cytology screening from 55 years to 75 years led to incremental decreases in cancer risk later in life. A 70-year old woman whose screening history was unknown had an average remaining lifetime risk of 1 in 588 (<1%; 95% percentile interval 1 in 451 to 1 in 873) if she stopped screening. Her remaining lifetime risk at age 70 years was reduced to 1 in 1206 (2·0 times reduction; 95% percentile interval 1 in 942 to 1 in 1748) if she had a negative cytology test, 1 in 6525 (12·9 times reduction; 95% percentile interval 1 in 3167 to 1 in 18 664) if she had a negative HPV test, and 1 in 9550 (18·1 times reduction; 95% percentile interval 1 in 4928 to 1 in 23 228) if she had a negative co-test for cytology and HPV.

Interpretation Cervical cancer risk reductions might be achieved by screening with cytology up to age 75 years, although with diminishing returns. A negative exit oncogenic HPV test or negative HPV test plus cytology correlates with a low remaining lifetime cervical cancer risk for unvaccinated women with a cervix after the age of 55 years.

Funding Canadian Institutes of Health Research.

Lancet Oncol 2018; 19: 1569–78

Published Online
November 1, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30536-9

This online publication has been corrected. The corrected version first appeared at thelancet.com/oncology on January 3, 2019

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Introduction

Human papillomavirus (HPV) vaccination has great potential to decrease cervical cancer incidence in the long term. However, older cohorts of women who have not benefited from vaccination will still depend on screening for the foreseeable future. The recommended age to stop cervical cancer screening generally varies between 50–70 years worldwide.[1] However, agencies making screening recommendations have recognised that the recommended age for last screening is based on low-quality evidence on the effectiveness of screening in older women.[2–4] Cervical cancer incidence and mortality remain high in older women—for example, US women aged 70 years and older have higher cervical cancer mortality (5·3–6·5 per 100 000 women) than do women aged 40–44 years (3·2 per 100 000 women).[5] There is evidence that women aged 65 years and older who undergo screening have lower cervical cancer incidence

Research in context

Evidence before this study

The American Society of Clinical Oncology (ASCO) expert panel previously did a high-quality systematic review of peer-reviewed evidence-based guidelines and recommendations on the screening and treatment of cervical precancerous lesions developed by multidisciplinary content experts and published between 1966 and 2015. They searched PubMed, SAGE, Cochrane Database of Systematic Reviews, and National Guideline Clearinghouse using search terms relating to "cervical intraepithelial neoplasia", "carcinoma", "mass screening", "evidence based", and "guidelines" or "recommendations". We considered the guidelines selected by the ASCO expert panel, and the guidelines published by the Canadian Task Force on Preventive Health Care and the US Preventive Service Task Force, to identify the evidence policy makers used worldwide to inform recommendations on the age at which to stop cervical cancer screening. Although most guidelines recommend that cervical cancer screening can be stopped after the age of 65–69 years in high-income settings, they also note the low-quality evidence this recommendation is based on. Many guidelines do not mention women who have had hysterectomies; some specify that women who have had a total hysterectomy should no longer be screened, but do not use cervical cancer incidence rates that exclude hysterectomies from the denominator when assessing the value of screening at older ages. Two guidelines referred to a modelling analysis as a source of evidence for their recommendations for the age at which to stop screening because of insufficient empirical evidence.

Added value of this study

Our study used a model of cervical cancer natural history calibrated to data to simulate the remaining lifetime risk of cervical cancer, addressing the paucity of empirical evidence for screening in older women. We projected the risks for women who stop screening at different ages and the long-term negative predictive value of an exit screen test, which would be very challenging to do with registry data or in an empirical study. We found that cervical cancers in later life, which might have been underestimated by policy makers because registry data generally do not remove women with hysterectomies from denominators, could be prevented in later life with cytology screening up to age 75 years. However, there is little benefit in screening women with a negative human papillomavirus (HPV) test after age 55 years, which holds true whether or not hysterectomies are taken into account.

Implications of all the available evidence

There are preventive benefits of screening women with a cervix using cytology up to around age 75 years, although these incremental benefits decline with age. A single negative HPV test provides strong reassurance against future risk of cervical cancer in older women exiting screening, as women negative for oncogenic HPV after age 55 years were predicted to be at low risk of cervical cancer for the rest of their lives.

than do women in the same age group who are not screened,[6,7] but whether this reduction is only a residual protective effect from having also been screened at younger ages is unclear. Opinions on the value of screening in older women have been divided.[8,9]

An often-overlooked issue in many screening guidelines is the prevalence of hysterectomies, which generally increases with age. Women who have had a total hysterectomy, including removal of the cervix, are no longer at risk for cervical cancer and need no longer be screened.[2–4] National cancer registries generally do not exclude women with hysterectomies from denominators for age-specific cancer incidence. Therefore, cervical cancer incidence might be substantially underestimated in older women with a cervix,[10–12] which could lead to underestimation of the benefits of screening in older women by policy makers, who depend on this registry data to determine cancer risk in older women.

Another important consideration is the increasing availability of oncogenic HPV testing, which will probably replace cytology as the main screening test for older women in many countries. A single negative HPV test has a very high predictive value and is associated with a 70% lower incidence of invasive cervical carcinoma compared with a negative cytology screen between the ages of 20–65 years.[13] However, most empirical evidence for HPV testing has focused on assessment of the safety of longer screening intervals. The risk of cervical cancer after an exit HPV test or negative HPV and cytology co-test at older ages remains unclear.

Because of an ageing world population, we could be confronted with increasing numbers of cervical cancers diagnosed at older ages, and an increased demand for prevention of diseases in these age groups.[14] In this study, we aimed to model the remaining lifetime risk of cervical cancer—for women with a cervix who stop screening at different ages and for different tests—to inform recommendations of the age at which to stop cervical cancer screening.

Methods

Study design and data sources

For this modelling study, we developed a state transition (Markov) model of cervical cancer natural history and screening. To ground our analyses in an empirical context, we calibrated and validated our model using Canadian provincial registries and survey data. Data sources are listed in the appendix (pp 8–12).

To simulate an age-structured population in the model, a new cohort of 236 564 women (one fifth of the population of Canadian women aged 20–24 in 2012) entered the model every year and were successively

See Online for appendix

modelled in parallel. Successive cohorts entered the model at age 10 years, creating an age-structured population. The time step of the model is 0·5 years. Women are assessed for background age-specific mortality (excluding cervical cancer deaths) at each time step. At the age of 100 years, all remaining living women were assumed to die. Incidence rates predicted by the model were age-standardised to the Canadian female population.

For this analysis, we did not model the effect of HPV vaccination as we focused on older birth cohorts. We assumed a background age-specific number of total hysterectomies for unrelated health reasons. If a woman had a total hysterectomy, she was assumed to be no longer at risk for cervical cancer. In the model, 42% of women who live until age 100 years will have a total hysterectomy, based on a Canadian population health survey by Statistics Canada.[15]

A detailed description of model structure, parameters, and development is in the appendix (p 4). Our research used aggregate secondary data sources, and thus did not require institutional review board approval.

Model description

For the development of the model, cervical cancer progression was divided into seven stages: uninfected, transient infection, persistent infection, cervical intra-epithelia neoplasia (CIN)1, CIN2, CIN3, and cervical cancer (figure 1). There is also a death state, to which all health states may transition each turn according to background mortality probabilities. As per these progression stages, uninfected women acquire transient HPV infections at an age-specific rate, which can eventually become persistent infections. Persistent HPV infections might progress sequentially to CIN 1–3. All CIN states can regress to persistent HPV infection. Women with CIN3 might progress to cervical cancer at an age-specific rate. We chose a three-stage progressive CIN model to include differences in management and treatment decisions depending on lesion severity. We modelled infections with four high-risk HPV groups: HPV16 and HPV18; HPV31, HPV33, HPV45, HPV52, and HPV58; HPV35, HPV39, HPV51, HPV56, HPV59, HPV66, and HPV68; and a generic group of other potentially oncogenic HPVs. Infection incidence, clearance, and oncogenic progression are group type-specific. Women infected with a less oncogenic HPV type could become infected with a more oncogenic type, the order of precedence being HPV16 and HPV18, followed by HPV31, HPV33, HPV45, HPV52, and HPV58, followed by HPV35, HPV39, HPV51, HPV56, HPV59, HPV66, and HPV68, followed by other HPVs.

All women in the model were assumed to have an average age-specific probability of being screened every year. The screening test has a probability of being positive according to the sensitivity and specificity of the test to a woman's underlying health state. Sensitivity and specificity are assumed to be independent of previous test results. We modelled the sensitivity and specificity of cytology.[16] Women who are screen-positive have a probability of their underlying lesion being treated; those who are not treated are retested with cytology every year. The probability of treatment is higher for high-grade lesions than for low-grade lesions. Women have a probability of being lost to follow-up (appendix p 10). If lost to follow-up, a woman does not attend scheduled treatments and follow-up, and returns to the general screening population. Cervical cancers have a probability of symptom development and detection outside screening. Women with detected cervical cancer have excess cervical cancer mortality, a background mortality from other causes, and a remission probability. Remission is defined as a state where treatment has succeeded in controlling the cancer to the point at which a woman no longer has excess mortality risk because of cervical cancer.

A full list of parameter values used for the development and calibration of the model is in the appendix (pp 8–10). We calibrated oncogenic progression and regression and the preclinical period of cervical cancer before development of symptoms to reproduce Canadian HPV infection prevalence by age,[17] CIN prevalence,[18] cervical cancer incidence by age,[19] and HPV type distribution in cervical cancer.[20] We sampled 40 000 combinations of values for oncogenic progression and regression probability and the preclinical period of cervical cancer by use of Latin Hypercube sampling. We ran the model with these 40 000 parameter sets, and calculated the

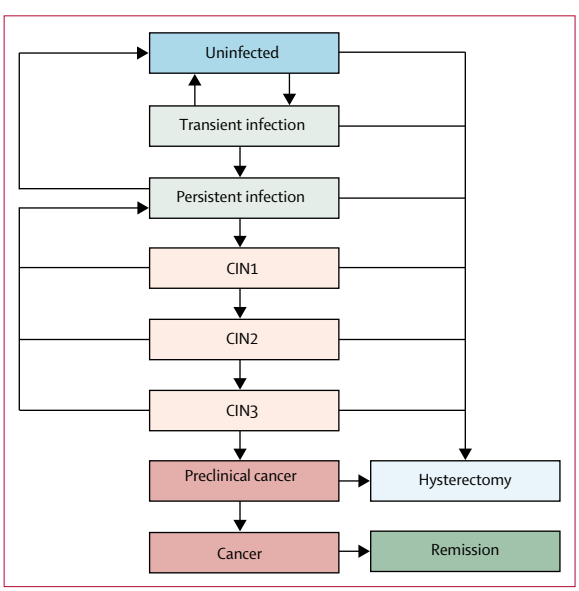

Figure 1: **Model natural history structure**
Boxes represent mutually exclusive health states and arrows represent possible transitions between health states. There is also a death state (not pictured) to which all health states could transition. Cohorts enter the model in the uninfected health state. CIN=cervical intraepithelial neoplasia.

log-likelihood that the empirical data were generated by that parameter set.

We used the log-likelihoods calculated with the 40 000 parameter sets to resample 3000 parameter sets with replacement. In this resample, there were 55 unique parameter sets reproducing HPV prevalence, screening outcomes, cervical cancer incidence, mortality, and cumulative lifetime risk of cervical cancer diagnosis in Canada (appendix p 12). To validate the model using these 55 parameter sets, we compared model predictions with different data not used during model calibration: Canadian type-specific HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, and HPV58 prevalence; abnormal Pap test risk; cumulative lifetime cervical cancer risk (1 in 152 women);[21] and cervical cancer incidence rates from the 1950s to 1960s before screening was widespread.

We used a base case scenario to represent a realistic assessment of risk for a typical woman, considering average screening attendance. Our base case scenario reflects actual cervical cancer screening adherence, with 53–68% of women aged 20–69 years being screened at least once in the past 42 months, depending on age.[18] Some women continue screening after age 69 years, but this proportion declines with age. We compared this base case to the following scenarios: no screening; perfect screening adherence (100% of women screened once every 3 years between the ages of 25–69 years, no screening in other age groups); and women with typical screening adherence stopping screening at various ages, conditional on having a negative screen test (cytology, HPV, or co-test). Scenarios assuming different stop ages of screening all assume the same typical screening participation up to the age at which screening stops. Cytology is assumed to have a sensitivity of 55% to detect CIN2+, consistent with large clinical trials and meta-analyses in the USA and Europe, correcting for verification bias.[16,22–24] HPV testing is assumed to have 100% sensitivity to detect HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV66, and HPV68. However, the sensitivity of HPV testing to detect CIN varies between parameter sets depending on HPV type distribution and is on average 91% for CIN2 and 97% for CIN3.

As part of model validation, we compared our model-predicted age-specific cervical cancer incidence without screening to historical data from the 1950s and 1960s, and found that model predictions were within observed ranges (appendix p 20).

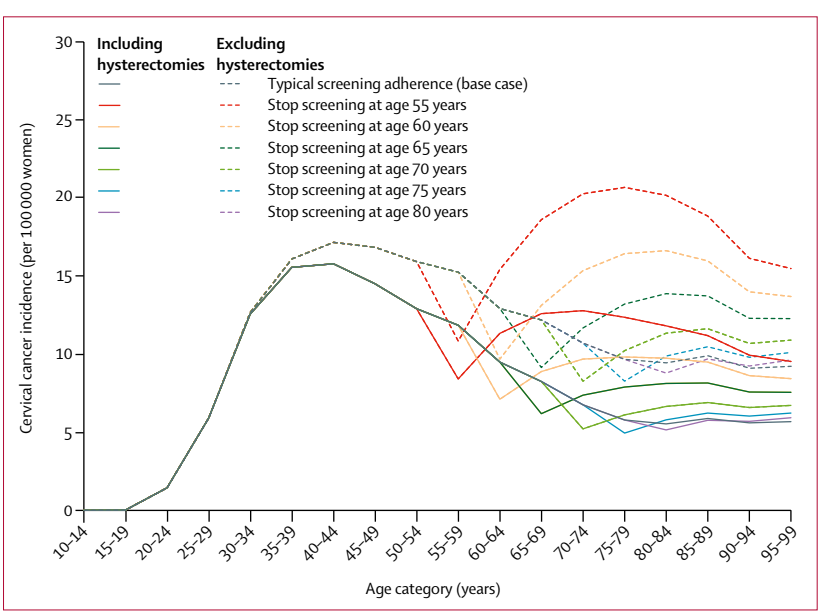

Figure 2: **Model-predicted age-specific cervical cancer incidence**
Lines show incidence when the denominator included (solid lines) and excluded (dashed lines) women with hysterectomies. Typical screening adherence refers to the base case scenario using average age-specific cytology screening. Other scenarios show model predictions if women have average age-specific cytology screening up to a given age, and then stop screening for the rest of their lives. Model predictions are the weighted average of 55 parameter sets.

Statistical analysis

We calculated cervical cancer incidence both including and excluding women who had hysterectomies from the denominator. For prospective risks in women with a cervix, the denominator is the number of women at a given age who have not yet undergone hysterectomy, and the numerator is the number of these women who are diagnosed with cervical cancer in the next 5, 10, or remaining lifetime years. Estimates of cumulative lifetime risk represent the risk from birth and therefore do not exclude hysterectomies (the denominator is the total size of the cohort at 10 years old).

We did sensitivity analyses varying the frequency of hysterectomies, varying the sensitivity of cytology (40% or 70%), doubling the prevalence of HPV in women aged 55 years and older, and restricting analyses to women with a true negative diagnosis for CIN or cancer (true normal). We did these sensitivity analyses to examine the potential effects of variations in hysterectomy numbers and cytology sensitivity across contexts, to investigate potential future increases in HPV prevalence in older age groups, and to approximate the risk of cancer after a long history of negative cytology screening.

We calculated mean model predictions over the selected 55 unique parameter sets and weighted according to the number of times they occurred in the 3000 parameter set resample. Variability across parameter set estimates is reported using the 95% percentile interval of predictions from the 55 parameter sets, presented as error bars or between 95% percentile intervals in brackets.

Statistical analyses were done with R (version 3.3.0).

Role of the funding source

The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We modelled cancer incidence with typical cytology screening adherence and hysterectomy numbers to investigate underestimation of cervical cancer incidence in at-risk women due to hysterectomies. The model suggests that the incidence of cervical cancer in women with a cervix is probably considerably underestimated in those aged 40 years and older when hysterectomies are not excluded from denominators (figure 2). Cervical cancer incidence that did not exclude women with hysterectomies from the denominator underestimated the incidence in women with a cervix by up to 71% in women aged 80–84 years.

The cumulative lifetime risk of cervical cancer is predicted to be much higher for women who will not be screened at any point in their lifetimes than for women with typical screening adherence, starting from age 30 years (figure 3). We estimate that without screening or vaccination, 1 in 45 women (95% percentile interval 1 in 32 to 1 in 64) would be diagnosed with cervical cancer in their lifetime. We predict that a woman with typical screening adherence with cytology who stops screening at age 55 years reduces her lifetime risk to 1 in 138 (95% percentile interval 1 in 109 to 1 in 188), and a woman with typical screening adherence who stops screening at age 70 years with cytology reduces her lifetime risk to 1 in 160 (95% percentile interval 1 in 127 to 1 in 213). This result suggests a substantial part of the reduction in the cumulative lifetime risk at older ages is due to screening before the age of 55 years (compared with no screening). We estimate that perfect adherence to cytology screening every 3 years from age 25–69 years would reduce the lifetime risk of cervical cancer to 1 in 532 women without HPV vaccination (95% percentile interval 1 in 375 to 1 in 820). We observed similar effects of screening when we estimated 10-year risk in women with a cervix at the start of each decade of their lives (figure 4).

We predicted the effect if all women stopped cytology screening at a given age, assuming no differences in screening practice up to that age (figures 2, 5). All scenarios led to a temporary decrease in cervical cancer incidence in the 5 years following the age at which screening stopped, because screening would no longer detect preclinical cervical cancerous lesions. This temporary decrease was followed by an increase in cervical cancer incidence in later life due to later symptomatic detection of latent cancers. Each 5-year delay in the age at which screening stopped, up until age 75 years, led to incremental reductions in later cervical cancer incidence. We predict that a woman with a cervix who stopped cytology screening at age 55 years will have around twice the 5-year risk of cervical cancer at age 70–85 years compared with a woman who continued screening with typical screening adherence.

We also estimated 5-year and remaining lifetime risks of cervical cancer for women with a cervix who stopped screening at a given age after a negative cytology test, a negative HPV test, or a negative co-test, assuming no differences in screening practice up to that age (figure 5, table). The model predicted that women with a cervix who test HPV DNA negative to 14 high-risk HPV types and stop screening at age 55 years have a remaining lifetime cervical cancer risk of 1 in 1940 (<1%), which is lower than the remaining lifetime risk for women with a cervix who test cytology negative (1 in 440 [<1%]) at the same age. The absolute risk for women with a negative co-test was similar to that for women with only a negative HPV test. Although an HPV DNA test alone missed lesions caused by other oncogenic HPV types, the model predicted that lesions caused by oncogenic HPV types not detected by the test had a low probability of progressing to cervical cancer in the remaining lifetime

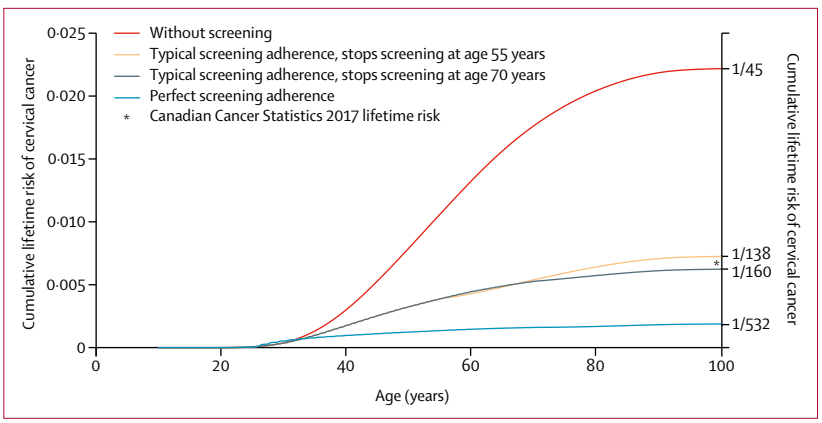

Figure 3: **Model-predicted cumulative cervical cancer lifetime risk**
Data show risk for no screening, typical screening adherence with screening stopped at specific ages, and perfect adherence. Estimates represent the crude lifetime risk at birth and therefore do not exclude hysterectomies (the denominator is the total size of the cohort at 10 years old). Scenarios where screening stops at age 55 years and 70 years assume average age-specific screening adherence up to these ages, and no screening thereafter. *Estimated lifetime risk of 1 in 152 for women in Canadian Cancer Statistics 2017.

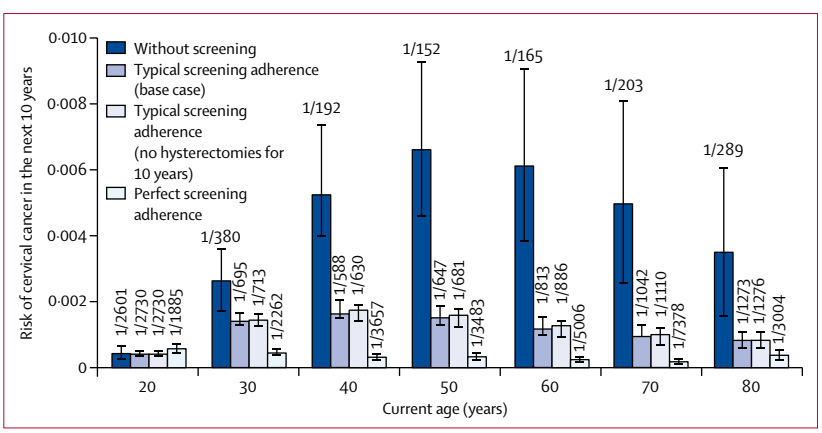

Figure 4: **Prospective risk of cervical cancer during the next 10 years for women with a cervix at a given age**
Data are the weighted mean and error bars represent 95% percentile interval of predictions of 55 unique parameter sets. Denominators are the number of women with a cervix at the start of each 10 years. Without screening indicates the risk for women with a cervix who are never screened. Typical screening adherence (base case) indicates the risk for women with average screening who currently have a cervix. Typical screening adherence (no hysterectomies for 10 years) indicates the risk for women with average screening adherence who currently have a cervix, and additionally assumes no hysterectomy during the next 10 years. Perfect screening adherence indicates the risk for women who currently have a cervix and who are screened with cytology every 3 years from age 25–69 years, at which point screening is stopped.

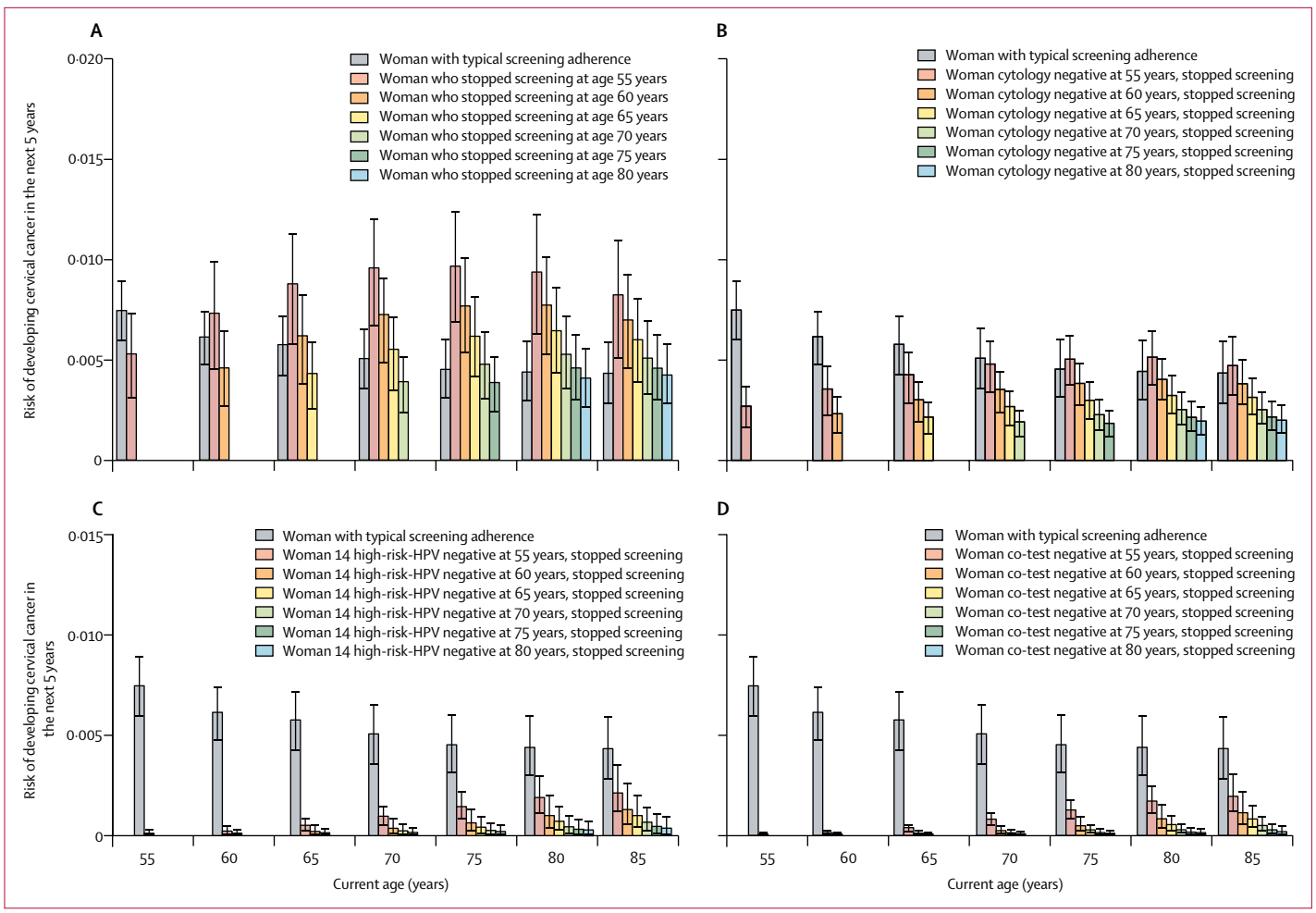

Figure 5: **Risk of developing cervical cancer in the next 5 years for women with typical screening adherence and who have a cervix, if screening is stopped at a given age**
Data are the weighted mean and error bars represent the 95% percentile interval of predictions of 55 unique parameter sets. Regardless of screening history (A), after a negative cytology result (B), after a HPV test negative for 14 high-risk HPV types (C), and after a negative co-test (D) (cytology and HPV test for 14 high-risk HPV types). We assumed the HPV test has 100% sensitivity to detect 14 oncogenic HPV types (HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV66, and HPV68). HPV=human papillomavirus.

(table). Women who stopped screening after a negative HPV test at age 55 years were predicted to have a lower remaining lifetime risk of cervical cancer (1 in 1940, 95% percentile interval 1 in 1271 to 1 in 3381; 1%) than women with the same typical screening adherence but who continued cytology screening up to age 70 years and then stopped after a negative cytology test (1 in 1206, 95% percentile interval 1 in 942 to 1 in 1748; <1%). Although women who have never been screened were predicted to be at higher risk of cervical cancer for the rest of their life compared with women with typical screening adherence, a single negative HPV test still indicated a relatively low remaining risk of cervical cancer after the age of 55 years (1 in 1096, 95% percentile interval 1 in 538 to 1 in 2401; <1%; table).

Women with a cervix at age 70 years who stopped screening had an average remaining lifetime cervical cancer risk of 1 in 588 (<1%; 95% percentile interval 1 in 451 to 1 in 873) without an exit screen test. Compared with women who had no exit screen test, women with a cervix at age 70 years who had an exit screening had an average remaining lifetime risk that is 1/2·0 (95% percentile interval 1/2·0 to 1/2·1) times lower after a negative cytology test, 1/12·9 (95% percentile interval 1/5·7 to 1/28·7) times lower after a negative HPV test, and 1/18·1 (95% percentile interval 1/9·0 to 1/37·3) times lower after a negative co-test (table). The absolute remaining lifetime risk of cervical cancer after a negative co-test was similar to the risk predicted for a true normal woman (true negative regarding diagnosis).

Analyses in the base case scenario assumed that a woman who has a cervix at a given age still has a future risk of hysterectomy within the next 5 or 10 years, and within her remaining lifetime. In sensitivity analyses, decreasing the number of hysterectomies did not substantially modify 10-year cervical cancer risk for women with a cervix, and only slightly increased the remaining lifetime risk after age 55 years (figure 4;

	Remaining lifetime risk after age 55 years			Remaining lifetime risk after age 70 years		
	Absolute risk		Relative risk*†	Absolute risk		Relative risk*†
Typical screening up to given age‡						
Stops screening	1/226 (<1%)	443/100 000 (310–544)*	1·0 (ref)	1/588 (<1%)	170/100 000 (115–222)*	1·0 (ref)
Cytology negative	1/440 (<1%)	227/100 000 (163–274)*	1/1·9 (1/1·8 to 1/2·0)	1/1206 (<1%)	83/100 000 (57–106)*	1/2·0 (1/2·0 to 1/2·1)
HPV test negative	1/1940 (<1%)	52/100 000 (30–79)*	1/8·9 (1/5·6 to 1/14·8)	1/6525 (<1%)	15/100 000 (5–32)*	1/12·9 (1/5·7 to 1/28·7)
Co-test negative	1/2253 (<1%)	44/100 000 (27–63)*	1/10·2 (1/6·8 to 1/15·7)	1/9550 (<1%)	10/100 000 (4–20)*	1/18·1 (1/9·0 to 1/37·3)
True normal§	1/2402 (<1%)	42/100 000 (28–57)*	1/10·8 (1/6·7 to 1/15·9)	1/13 678(<1%)	7/100 000 (4–11)*	1/24·8 (1/12·5 to 1/40·0)
Never screened before¶						
Remains unscreened	1/66 (2%)	1525/100 000 (997–2130)*	1·0 (ref)	1/125 (1%)	803/100 000 (480–1150)*	1·0 (ref)
Cytology negative	1/120 (1%)	830/100 000 (599–1109)*	1/1·8 (1/1·6 to 1/2·0)	1/246 (<1%)	407/100 000 (261–575)*	1/2·0 (1·8^{-1} to 2·0^{-1})
HPV test negative	1/1096 (<1%)	91/100 000 (42–186)*	1/18·2 (1/9·6 to 1/40·0)	1/2167 (<1%)	46/100 000 (11–110)*	1/21·3 (9·2^{-1} to 93·5^{-1})
Co-test negative	1/1504 (<1%)	66/100 000 (34–120)*	1/24·1 (1/14·9 to 1/45·4)	1/3838 (<1%)	26/100 000 (8–59)*	1/36·3 (1/17·1 to 1/122·7)

Data assume typical screening adherence up to age 55 years or 70 years, or no previous screening. Data are the weighted mean of 55 unique parameter sets. HPV=human papillomavirus. *Numbers in brackets are the 95% percentile interval of predictions of 55 parameter sets. †Relative risks less than 1 are expressed as inverses. Denominators greater than 1 reflect how many times the risk is lower relative to the reference case. ‡Risk for a woman with a cervix with average lifetime screening up to age 55 years or 70 years, who stopped screening without considering previous test results (stops screening) or who received a negative exit screen test result. §Hypothetical scenario of remaining lifetime risk for a true cytologically normal woman with a cervix at age 55 years or 70 years who stopped screening. Reflects the maximum potential risk reduction if a long history of negative cytology tests is assumed to identify true normal women. ¶Risk for a woman with a cervix who has never been screened before, and who will remain never screened (remains unscreened) or who received a negative screen result for the first time at a given age.

Table: **Predicted remaining lifetime risk of cervical cancer for a woman with a cervix who stops screening at age 55 years or 70 years**

appendix p 2). The absolute remaining lifetime risk of cervical cancer increased when we assumed a two-times higher prevalence of high-risk HPV in women aged 55 and over. However, the relative risk of cervical cancer after an exit screen test remained similar (appendix p 2). This suggests potential increases in HPV prevalence in older age groups because of cohort effects would not materially change conclusions. The absolute risk of cervical cancer after a negative exit cytology screen increased when we assumed a lower sensitivity of cytology. The absolute risk of cervical cancer after a negative exit HPV test or co-test was not substantially affected by the sensitivity of previous cytology screening up to that age (appendix p 2).

Discussion

Whether reductions in cervical cancer incidence at older ages are due to cumulative prevention from screening at younger ages and whether screening at older ages provides additional benefits have been debated.6–9 We used a model of cervical cancer natural history to address the paucity of empirical evidence for screening in older women. Our results suggest that most of the prevention of cervical cancer in later life is due to screening before the age of 55 years, but continued cytology screening up to around age 75 years can still lead to incremental decreases in cancer risk in later life. However, women who have a negative high-risk HPV test or co-test after the age of 55 years were predicted to be at low risk for cervical cancer for the rest of their lives, with lower risk than women who continued cytology screening with typical adherence. Models of cervical cancer natural history, such as that in the present study, may be useful for policy decision analyses when long-term empirical evidence is challenging to acquire, and thus might help estimate the long-term health effects of intervention. The US Preventive Services Task Force previously used a modelling framework to support its latest cervical cancer screening recommendations because of the paucity of empirical evidence in older women.[25] Similar to ours, this previous modelling analysis found that the small incremental gains in life expectancy from cytology screening were expected to start tapering off between the ages of 65 years and 75 years.[25] However, some screening after the age of 65 years might still be cost-effective in a cytology screening context.[26]

We calibrated the calculated risks to be applicable to current generations of older women in developed countries with longstanding screening programmes, who up until recently lived most of their lives in a cytology screening context and were unlikely to be vaccinated against HPV. Because we conditioned our analyses on women having a cervix at each age, our conditional risk estimates should not be sensitive to

differences in hysterectomy numbers between countries and over time.[12] The absolute risk of cervical cancer after exit cytology screening depended on the assumed cytology test sensitivity in our analyses. However, the risk after a negative exit HPV test or co-test was not substantially affected by the sensitivity of previous cytology screening up to the age of the exit screen. This factor suggests that although the absolute risk of cervical cancer at older ages might vary across screening contexts depending on achieved screening sensitivity, the risk after a negative HPV test is much less likely to be context-dependent. Our results might not be applicable to future cohorts with high vaccination coverage or who will have been screened for most of their lives with HPV testing. However, as it will be many decades before cohorts vaccinated as adolescents reach the age of 50–70 years, our results are likely to be applicable to older cohorts of women for years to come.

Cervical cancer incidence in registries often does not exclude women with hysterectomies from denominators.[5,19] Registry cervical cancer incidence that includes women with hysterectomies in denominators is probably affected by worldwide variations in age at which screening stops and the prevalence of hysterectomy.[12] We calibrated our model to Canadian age-specific cervical cancer incidence, so our absolute risk estimates are most reflective of the Canadian context. However, the model-predicted relative effects of stopping screening at different ages should be generalisable to most developed countries with longstanding screening programmes. For example, our model-predicted cancer incidence when cytology screening was stopped at age 60 years gave similar age-specific patterns to those reported in Finland[27] and the Netherlands,[28] both of which have organised screening programmes that stop at age 60 years and low numbers of hysterectomies. The rebound in cervical cancers at older ages might be absent in Canadian and American registries because of a more gradual decline in screening participation reported with age and higher hysterectomy prevalence.[5,15]

A limitation of our analysis is that, like most cervical cancer models, we calibrated oncogenic progression risk to current age-specific cancer and HPV patterns, assuming no cohort effects. Age–cohort–period models suggest that the background risk of cervical cancer has increased in successive birth cohorts since the mid-20th century (possibly because of changes in sexual behaviours), while increased screening has reduced the cervical cancer risk over time.[7,29,30]

Using decision models to account for these cohort effects is challenging because of a paucity of comparable age-specific data on how hysterectomy use, screening participation, and HPV prevalence have changed over time since the 1940s. For example, the observed cervical cancer incidence in women aged 75–85 years is slightly higher than that predicted by our model, probably because women in these cohorts were less exposed to screening than younger women throughout their lifetime. To verify whether this biased our risk estimates, we compared our results for cancer incidence without screening to historical data from the 1950s and 1960s and found a good match (model predictions were within the range of observed historical age-specific cervical cancer incidence; appendix p 20). Despite cohort and period effects, these findings suggest that our model reproduces the oncological progression from infection to cervical cancer and the risk of cervical cancer with and without screening well. Our results therefore might be interpreted as the predicted future age-specific risk of cervical cancer, assuming current participation in screening continues in the future. Our sensitivity analyses suggest that future increases in HPV prevalence due to differences in sexual behaviours between cohorts would also not substantially change our results. Another potential limitation of our model is that we assumed all women to have the same average screening probability with the same test sensitivity. We therefore probably underestimated the number of women who are never screened or who have hard to detect lesions in the base case analysis. To address this limitation, we evaluated scenarios with no screening and with lower cytology sensitivity to provide cervical cancer risk estimates for these categories of women.

Few studies of HPV infection and oncogenic progression have included older women. We therefore assumed that progression risks from infection to CIN in older women are similar to those measured in younger women. Epidemiological studies do not suggest that type-specific progression from an infection varies substantially with age after conditioning on HPV type,[31–33] but, to our knowledge, no studies have focused on older women specifically. Newly detected infections generally have a low risk of progressing to CIN in older women.[33] If oncogenic progression declines with age, then the remaining lifetime risk of cervical cancer would be even lower after a negative cytology or HPV test than predicted by our model.

Because of the low sensitivity of a single cytology screen some guidelines recommend a woman only stop screening after a sufficient history of negative screens.[2,3] We did not assess this strategy, as a limitation of our model is that it does not track the screening histories of women. Nonetheless, as many women do not adhere to the recommended screening intervals, it is likely many will reach the age at which screening ends with an unknown or inadequate screening history. We found that for a typical woman with average screening adherence, a single negative cytology test below age 70 years did indeed not provide substantial reassurance of a long-term reduction in cancer risk. Therefore, additional screening might be warranted for a woman with an inadequate screening history in a cytology screening context. However, we found that a single negative HPV test or co-test after age 55 years indicated a very low remaining lifetime risk of cervical cancer. Although

women older than 55 years might have new HPV infections or latent virus reactivations later in life, our model predicts that these infections in most cases would not have time to progress to cervical cancer within such women's lifetimes. These results align with empirical data in younger women, showing the negative predictive value of a negative HPV test is much higher than that of a normal cytology test.[13,34]

What constitutes a sufficiently low risk of cervical cancer to stop screening has no definitive answer and will depend on societies' and individuals' risk tolerance and available resources. It has been proposed that guidelines could use the risk implicit in existing accepted practice as a benchmark.[35] Countries might therefore use their current remaining lifetime cervical cancer risk after the age at which they recommend ending screening as their upper risk threshold (eg, the current crude risk of cervical cancer after age 70 years in Canada is around 0·3%).[21] Alternatively, a stricter benchmark might be the risk of cervical cancer within a country's recommended screening interval—for example, it has been estimated that the risk of cervical cancer 3–5 years after a negative cytology screen is 0·017–0·025% for US women aged 30–64 years;[35] therefore, risks below this threshold could be considered consistent with the risk tolerance for a 3–5 year screening interval. The balance of harms and benefits of screening is another important consideration for any screening programme.[2,3] The harms of screening older women include potential stress, pain, and discomfort caused by screening and false-positive results, and the costs of extending screening.

Due to ageing populations, there is likely to be increased demand for prevention of diseases in older age groups. Therefore, it is important to consider the added value of screening at older ages. Cervical cancer screening between the ages of 30–49 years should be the priority,[4] as this strategy prevents the most cervical cancer cases. However, our model predicts that there are also incremental benefits to continuing screening for women after these ages, although these benefits decline with age. Screening recommendations should not be made solely on the basis of cervical cancer incidence, which includes women with hysterectomies in the denominator, because this does not necessarily reflect cancer risk in older women with a cervix who are currently the target of screening programmes. Importantly, we found that an exit HPV test provides strong reassurance against cervical cancer past the age of 55 years, as women who test negative for high-risk HPV were predicted to be at very low risk of cervical cancer for the rest of their lives.

Contributors

TM developed and calibrated the model. SK, ELF, M-HM, GO, LS, WG, and CB reviewed model structure and parametric assumptions. GO provided data for model calibration. TM, SK, and ELF designed the analysis, and M-HM, GO, LS, WG, and CB provided crucial feedback on the analysis plan. TM ran the simulations, did the analysis, and wrote the first draft of the manuscript. All authors reviewed the manuscript for intellectual content.

Declaration of interests

TM reports research funding from the Canadian Institutes of Health Research (CIHR) during the conduct of the study. ELF reports research funding from CIHR during the conduct of the study, grants from Merck, grants and non-financial support from Roche, personal fees from Merck, and personal fees from GlaxoSmithKline outside the submitted work. M-HM is a recipient of a Fonds de Recherche du Québec—Santé clinical research scholar salary award. CB has received speaker honoraria from Merck Canada and is a member of the advisory boards for Merck Canada and Pfizer Canada. GO reports grants from Roche Molecular Systems and Gen Probe outside the submitted work. All other authors declare no competing interests.

Acknowledgments

This work was supported by the Canadian Institutes of Health Research (operating grant 68893, team grant 83320, and catalyst grant HSE-151297 to ELF, and Fellowship Award to TM).

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Malagón T, Kulasingam S, Mayrand M-H, et al. Age at last screening and remaining lifetime risk of cervical cancer in older, unvaccinated, HPV-negative women: a modelling study. *Lancet Oncol* 2018; published online Nov 1. http://dx.doi.org/10.1016/S1470-2045(18)30536-9.

SUPPLEMENTARY APPENDIX

Age of last screening and the remaining lifetime risk of cervical cancer after a negative cytology or HPV test in older unvaccinated women: a model-based analysis

SUPPLEMENTARY TABLE

Supplementary Table 1. Sensitivity analyses of remaining lifetime risk of cervical cancer for a woman with a cervix and with typical screening adherence who stops screening at age 55 or 70, weighted mean of 55 parameter sets.

	Remaining lifetime risk after age 55				Remaining lifetime risk after age 70			
	Absolute risk				Absolute risk			
Scenario	**1 in:**	**%**	**per 100,000[a]**	**Relative risk[a,b]**	**1 in:**	**%**	**per 100,000[a]**	**Relative risk[a,b]**
No remaining lifetime risk of hysterectomy[c]	184	0.54%	534 [385-668]	1·0 [ref]	535	0.19%	187 [126-244]	1·0 [ref]
Cytology negative	357	0·28%	280 [203-338]	1/1·9 [$1·8^{-1}$ to $2·0^{-1}$]	1098	0·09%	91 [63-117]	1/2·0 [$2·0^{-1}$ to $2·1^{-1}$]
HPV test negative	1478	0·07%	68 [39-103]	1/8·3 [$5·3^{-1}$ to $13·8^{-1}$]	5868	0·02%	17 [6-35]	1/12·8 [$5·6^{-1}$ to $28·2^{-1}$]
Co-test negative	1703	0·06%	59 [37-83]	1/9·5 [$6·3^{-1}$ to $14·5^{-1}$]	8562	0·01%	12 [5-23]	1/17·8 [$8·9^{-1}$ to $36·7^{-1}$]
Hysterectomy rates reduced by half[c]	200	0.50%	499 [352-613]	1·0 [ref]	555	0.18%	180 [122-235]	1·0 [ref]
Cytology negative	389	0·26%	257 [186-310]	1/1·9 [$1·8^{-1}$ to $2·0^{-1}$]	1138	0·09%	88 [61-113]	1/2·0 [$2·0^{-1}$ to $2·1^{-1}$]
HPV test negative	1650	0·06%	61 [35-92]	1/8·5 [$5·4^{-1}$ to $14·2^{-1}$]	6108	0·02%	16 [6-34]	1/12·8 [$5·6^{-1}$ to $28·4^{-1}$]
Co-test negative	1907	0·05%	52 [33-74]	1/9·7 [$6·5^{-1}$ to $14·9^{-1}$]	8923	0·01%	11 [5-22]	1/17·9 [$8·9^{-1}$ to $36·9^{-1}$]
HPV prevalence doubled[c,d]	208	0.48%	482 [343-584]	1·0 [ref]	482	0.21%	208 [147-259]	1·0 [ref]
Cytology negative	383	0·26%	261 [193-314]	1/1·8 [$1·7^{-1}$ to $1·9^{-1}$]	1118	0·09%	89 [62-112]	1/2·3 [$2·3^{-1}$ to $2·4^{-1}$]
HPV test negative	1162	0·09%	86 [53-124]	1/5·7 [$3·9^{-1}$ to $8·7^{-1}$]	4569	0·02%	22 [10-39]	1/10·2 [$5·8^{-1}$ to $19·7^{-1}$]
Co-test negative	1266	0·08%	79 [51-109]	1/6·2 [$4·2^{-1}$ to $9·0^{-1}$]	5864	0·02%	17 [9-28]	1/12·8 [$8·1^{-1}$ to $22·1^{-1}$]
Cytology sensitivity 40%[c,e]	163	0.62%	615 [457-758]	1·0 [ref]	386	0.26%	259 [188-331]	1·0 [ref]
Cytology negative	248	0·40%	404 [303-497]	1/1·5 [$1·5^{-1}$ to $1·5^{-1}$]	600	0·17%	167 [122-213]	1/1·6 [$1·5^{-1}$ to $1·6^{-1}$]
HPV test negative	1729	0·06%	58 [32-94]	1/11·1 [$6·7^{-1}$ to $19·3^{-1}$]	5042	0·02%	20 [6-42]	1/15·5 [$6·5^{-1}$ to $41·1^{-1}$]
Co-test negative	1971	0·05%	51 [29-78]	1/12·5 [$8·1^{-1}$ to $20·4^{-1}$]	6711	0·01%	15 [5-31]	1/20·0 [$9·1^{-1}$ to $46·8^{-1}$]
Cytology sensitivity 70%[c,e]	308	0.32%	325 [219-407]	1·0 [ref]	879	0.11%	114 [75-149]	1·0 [ref]
Cytology negative	782	0·13%	128 [92-155]	1/2·5 [$2·2^{-1}$ to $2·8^{-1}$]	2494	0·04%	40 [27-52]	1/2·8 [$2·6^{-1}$ to $3·0^{-1}$]
HPV test negative	2118	0·05%	47 [28-69]	1/7·1 [$4·5^{-1}$ to $11·4^{-1}$]	8087	0·01%	12 [5-25]	1/10·5 [$4·9^{-1}$ to $22·3^{-1}$]
Co-test negative	2456	0·04%	41 [26-56]	1/8·2 [$5·1^{-1}$ to $12·2^{-1}$]	12507	0·01%	8 [4-15]	1/15·5 [$8·3^{-1}$ to $29·2^{-1}$]

HPV=human papillomavirus; max=maximum; min=minimum; ref=reference scenario.

[a] Numbers in brackets are the 95% percentile interval of predictions of 55 parameter sets.

[b] Relative risks lower than 1 are expressed as inverses: denominators above 1 reflect how many times the risk is lower relative to the reference case.

[c] Average risk for a woman with a cervix who stops screening at age 55 or 70 regardless of screening history, assuming average lifetime screening rates up to that age

[d] Oncogenic HPV prevalence in women 55 and over is assumed to be two times higher than in the base case scenario.

[e] These scenarios assumed the cytology sensitivity was 40 or 70% both throughout the woman's life and during the exit screen test.

CANADIAN CERVICAL CANCER NATURAL HISTORY AND SCREENING MODEL DESCRIPTION, PARAMETERS, CALIBRATION, & VALIDATION

Version: February 23rd 2018

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1 MODEL DESCRIPTION

1.1 Structure

We programmed a Markov state-transition model of human papillomavirus (HPV) and cervical cancer natural history and screening using base R (https://www.R-project.org/). This model was adapted to the Canadian context to inform cervical cancer screening decision-making.

1.1.1 Demographics

Women enter the model at the age of 10 years. The time step of the model is 0·5 years. Women are subject to background age-specific Canadian mortality rates (excluding cervical cancer deaths) at each time step. At the age of 100, all remaining living women die.

A new cohort of women enters the model every year. Successive cohorts are modelled in parallel in order to simulate an age-structured population. Each year's cohort is of 236,564 women (1/5 of the population of Canadian women aged 20-24 in 2012). Incidence rates predicted by the model will be age-standardized to the Canadian female population.

1.1.2 Natural history

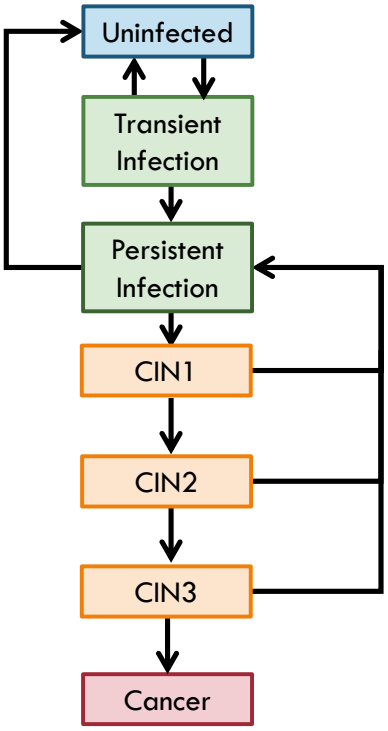

Figure 1. Natural history of cervical cancer without any intervention.

The natural history of cervical cancer has been divided into 7 underlying health states: **Uninfected**, **Transient Infection**, **Persistent Infection**, **CIN1**, **CIN2**, **CIN3**, and **Cervical Cancer** (Figure 1). There is also a **Death** state, to which all health states may transition each turn according to background mortality probabilities (not pictured in Figure 1). **Cervical Cancer** also has additional cancer-related mortality, described below in *Cancer Treatment and Survival*.

Uninfected women may at first acquire a **Transient Infection**, which may eventually become a **Persistent Infection** if it is not cleared. Only **Persistent Infections** may progress sequentially to **CIN1**, **CIN2**, and **CIN3**. All **CIN** states may regress back to a state of **Persistent Infection**. Women with **CIN3** may progress to **Cervical Cancer** at an age-specific rate. Women with **Cervical Cancer** cannot regress.

The natural history of infection with four high risk (HR) HPV type groups is modeled: **HPV16/18**, **HPV31/33/45/52/58**, **HPV35/39/51/56/59/66/68**, **Other HR**. These groups were chosen based on carcinogenicity, inclusion in HPV vaccines, and inclusion in the cobas® 4800 HPV assay which has been approved as a screening test in many jurisdictions.[1] **Uninfected** women can become infected with any one of these four group types according to age-specific and group type-specific infection rates. Infection incidence rates, clearance rates, and oncogenic progression rates are group type-specific.

Women with a **Transient Infection** or **Persistent Infection** with a less oncogenic type may become infected with a more oncogenic type, the order of precedence being **HPV16/18 > HPV31/33/45/52/58 > HPV35/39/51/56/59/66/68 > Other HR**. The oncogenic progression risk then becomes the one of the most oncogenic type. For women in **CIN** and **Cervical Cancer** states we do not model the risk of becoming infected with a higher risk type as they are already on an oncogenic progression pathway.

1.1.3 Hysterectomies

We assume a background age-specific rate of hysterectomies for health reasons unrelated to cervical cancer (Figure 2). Screening does not affect this hysterectomy rate. Once a woman is in the **Hysterectomy** state, she is assumed to be no longer at risk for cervical cancer, and therefore can only exit the model through death from other causes. As not all hysterectomies remove the cervix, we adjusted the hysterectomy rate to reflect only total hysterectomies.

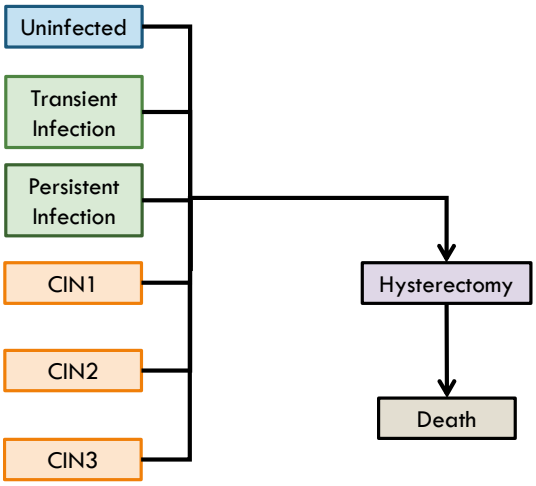

Figure 2. Background hysterectomies.

The age-specific probabilities of hysterectomy were calculated to reproduce the cumulative smoothed proportion of women by age that self-report having had a hysterectomy (Figure 3).[2] In the model, 42% of women who live until the age of 100 will have had a total hysterectomy.

Though screening is not recommended for women who have had a total hysterectomy, evidence suggests that many women who have had a hysterectomy still get screened despite recommendations.[3] We therefore included in the model a yearly probability of screening women with hysterectomies.

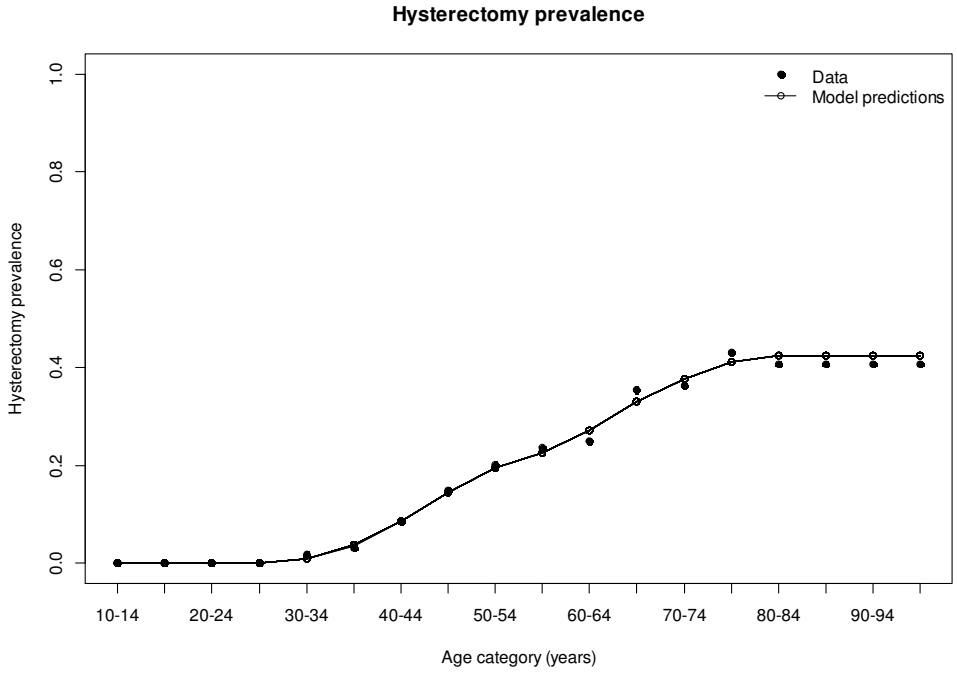

Figure 3. Age-specific cumulative proportion of women having had a total hysterectomy.
The line (Model) represents the modelled prevalence of hysterectomy compared to the points (Data) which are the self-reported hysterectomies in the Canadian Community Health Survey 2014 annual component.[2] We assumed 84% of hysterectomies were total hysterectomies based on Toma *et al.* (2004).[4]

1.1.4 Detection of health states through screening and symptoms

The model distinguishes between Undetected (or preclincial) health states, and Detected health states that have been detected through screening or symptoms. Screening operates by causing Undetected health states to become Detected health states in the model (Figure 4).

Women in Undetected health states (the regular screening population) have an age-specific probability of being screened every year. For screened women, the screening test has a probability of being positive according to the sensitivity and specificity of the test to her underlying health state. If the test is positive, the undetected health state becomes a detected health state that will be followed-up and managed. In order to reproduce historical epidemiological data, we currently model the sensitivity and specificity of cytology. The probability of being test-positive for **Uninfected**, **Transient Infections**, and **Persistent Infections** is 1-Specifity. The probability of being test-positive for **CIN1** is the sensitivity of the test to low grade lesions. The probability of being test positive for **CIN2**, **CIN3**, and **Cervical Cancer** is the sensitivity of the test to high grade lesions.

Preclinical Cervical Cancers (undetected cancers) have an additional probability of developing symptoms and being detected outside of regular screening.

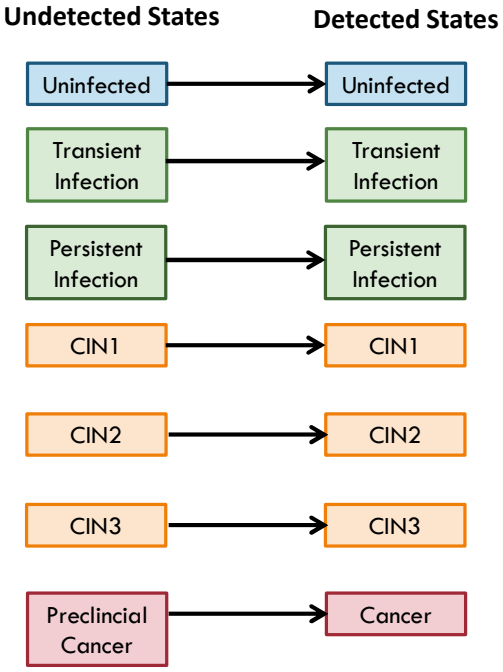

Figure 4. Screening and symptoms transform Undetected states into Detected states.

1.1.5 CIN treatments

Once screen-positive, women have a probability of being sent to colposcopy and have any underlying lesion treated. This probability depends on a woman's age and the degree of severity of the detected lesion. The probability of getting sent to colposcopy is higher for high grade lesions than for low grade lesions; however it is assumed a certain minority of persistent low-grade lesions will be sent to colposcopy and treated[5]. Treatment is only performed if women return for follow-up (see next section).

Three outcomes of treatment are possible: 1) the treatment succeeds in removing both the lesion and the underlying infection, upon which the woman returns to the **Uninfected** state; 2) the treatments succeeds in removing the lesion but not the infection, upon which the woman returns to the **Persistent Infection** state; or 3) the treatment fails and the lesion is not removed. When the treatment fails, the lesion's natural history is unchanged and it may progress, regress, or persist as it would have done without treatment. Treatment failure does not depend on lesion grade. Potential treatment outcomes for **CIN3** are presented as an example in Figure 5.

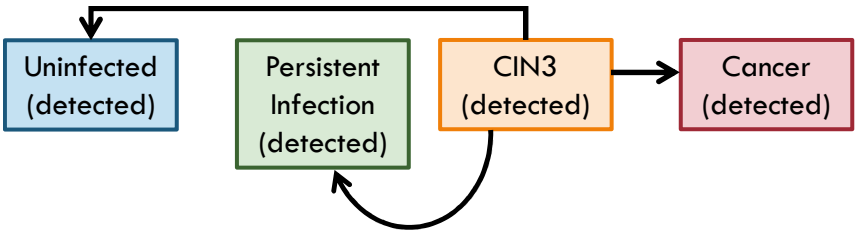

Figure 5. CIN treatment outcomes, using CIN3 as an example.
CIN3 that does not get removed by treatment has the same probability of progressing to Cancer or regressing to Persistent Infection in absence of treatment.

1.1.6 Follow-up and return to regular screening of screen-positive women

Once screen test-positive, women have a probability each time step of being lost to follow-up. Once lost to follow-up, she does not attend scheduled treatments and rescreenings. Her health state switches from Detected to Undetected, meaning she returns to the regular screening population whose underlying health state is unknown with average yearly screening probabilities (Figure 6). The probability of being lost to follow-up depends on a woman's age and underlying health state, with higher grade lesions less likely to be lost to follow-up.

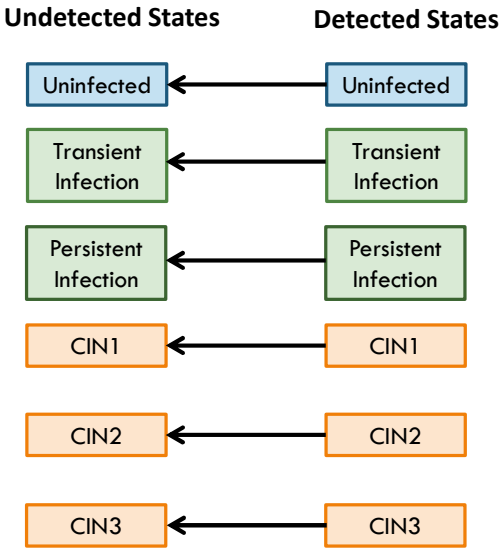

Figure 6. Loss to follow-up and returns to the regular screening population.

Women who are screen test-positive, who are not lost to follow-up, and who are not scheduled for colposcopy/treatment undergo repeat rescreening every year. If the rescreen test is positive, they once again have a chance to be sent to colposcopy and treatment. If the rescreen is negative, their health state switches from Detected to Undetected, and they return to the regular screening population with average yearly screening probabilities. Women who have been treated for **CIN** are also rescreened every year until the rescreen test is negative, upon which they return to regular screening. We currently model cytology as the rescreen test, and assume the rescreen has the sensitivity and specificity of cytology.

Detected health states under active surveillance have the same probabilities of progression, regression, and persistence as undetected health states. The natural history of cervical cancer progression is therefore not modified by screening unless a woman receives treatment.

1.1.7 Cancer treatment and survival

A cervical cancer is only counted in the cancer incidence rate once it is detected. Therefore, a woman who dies from other causes with a **Preclincial Cervical Cancer** would not contribute to cervical cancer incidence and mortality rates. Excess mortality due to cervical cancer and potential treatments only occur once the **Cervical Cancer** state has been detected through screening or symptoms (Figure 7).

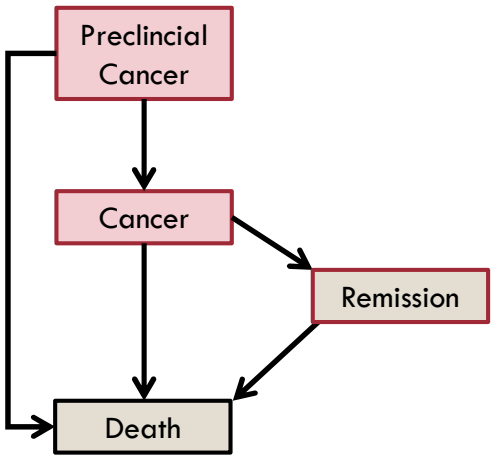

Figure 7. Cancer treatment and survival.

Women with detected **Cervical Cancer** have a probability of dying of background causes of death plus an additional probability of dying of cervical cancer each time step. If a woman does not die, she has a probability of going into remission due to treatment. **Remission** is assumed to be a state where treatment has succeeded in controlling the cancer to the point where the woman no longer has excess mortality risk due to cervical cancer. Women in the **Remission** health state therefore only have age-specific background mortality risks and do not contribute to cervical cancer mortality. Women in **Remission** are assumed to be no longer at risk for cervical cancer. This health state was added because women who have survived cervical cancer for 5 years have nearly the same net mortality rate as the general population of women of the same age,[6] suggesting treatment has effectively reduced the cancer mortality risk for many women.

We do not model cancer stage, but instead use age-specific cancer remission probabilities to account for the fact that younger women have higher net 5-year cancer survival than older women (see below for further details).

1.2 Parameters

Parameters determine the probability of transitioning between health states in the model (Table A2). Where possible, Canadian population data sources were used to inform model parameters. Where possible, we used data from the year 2012, as this was the most recent year available in many CANSIM tables at the time of model development and corresponds to a time period before HPV vaccination is likely to have substantially impacted screening outcomes. If Canadian data was unavailable, values were supplemented with data from other developed countries. This is a tenable assumption because these data are assumed to be either context-independent (HPV infection duration) or to be very similar across developed countries (HPV prevalence in children and elderly adults, cytology sensitivity, CIN treatment failure). Values for parameters marked as "calibrated" were derived from calibration procedures described in the next section (*Calibration*).

More detailed notes for the calculation of particular parameters can be found at the end of this Appendix.

Table A2. Model parameter values and data sources.

Parameter	Age (years)	Value	Data source	Canada data	Ref.
Demography					
Cohort size each year	10	236,564	CANSIM Table 051-0001 (2012)	✓	7
Background death rates (/1,000 years)	10-14	0·1	CANSIM Table 102-0504 (2012)	✓	8
	15-19	0·3	CANSIM Table 102-0504 (2012)	✓	8
	20-24	0·3	CANSIM Table 102-0504 (2012)	✓	8
	25-29	0·3	CANSIM Table 102-0504 (2012)	✓	8
	30-34	0·4	CANSIM Table 102-0504 (2012)	✓	8
	35-39	0·6	CANSIM Table 102-0504 (2012)	✓	8
	40-44	0·9	CANSIM Table 102-0504 (2012)	✓	8
	45-49	1·6	CANSIM Table 102-0504 (2012)	✓	8
	50-54	2·4	CANSIM Table 102-0504 (2012)	✓	8
	55-59	3·9	CANSIM Table 102-0504 (2012)	✓	8
	60-64	5·8	CANSIM Table 102-0504 (2012)	✓	8
	65-69	9·2	CANSIM Table 102-0504 (2012)	✓	8
	70-74	14·5	CANSIM Table 102-0504 (2012)	✓	8
	75-79	24·3	CANSIM Table 102-0504 (2012)	✓	8
	80-84	44·4	CANSIM Table 102-0504 (2012)	✓	8
	85-89	82·1	CANSIM Table 102-0504 (2012)	✓	8
	90+	180·5	CANSIM Table 102-0504 (2012)	✓	8
Hysterectomy risk (/0·5 year)	<30	0·0%	CCHS 2014 Annual Component	✓	2
	30-34	0·2%	CCHS 2014 Annual Component	✓	2
	35-39	0·4%	CCHS 2014 Annual Component	✓	2
	40-44	0·6%	CCHS 2014 Annual Component	✓	2
	45-49	0·7%	CCHS 2014 Annual Component	✓	2
	50-54	0·5%	CCHS 2014 Annual Component	✓	2
	55-59	0·3%	CCHS 2014 Annual Component	✓	2
	60-64	0·8%	CCHS 2014 Annual Component	✓	2
	65-69	0·8%	CCHS 2014 Annual Component	✓	2
	70-74	0·6%	CCHS 2014 Annual Component	✓	2
	75-79	0·5%	CCHS 2014 Annual Component	✓	2
	80+	0·0%	CCHS 2014 Annual Component	✓	2
Natural history					
All HPV types					
HPV incidence rate (/100 year)	10-14	1·7	Survey of unvaccinated Scottish adolescents (fitted)		9
Regression CIN1>Persistent Infection	All	Calibrated	Ontario Cancer Registry	✓	10
Regression CIN2>Persistent Infection	All	Calibrated	Ontario Cancer Registry	✓	10
Regression CIN3>Persistent Infection	All	Calibrated	Ontario Cancer Registry	✓	10
HPV16/18					
Median infection duration (months)	All	15·7	Placebo arm of HPV vaccine trial		11
Incidence rate (/100 year)	15-19	8·0	BC screening population (fitted)	✓	12
	20-24	8·1	BC screening population (fitted)	✓	12
	25-29	2·6	BC screening population (fitted)	✓	12
	30-34	1·6	BC screening population (fitted)	✓	12
	35-39	0·6	BC screening population (fitted)	✓	12
	40-44	0·9	BC screening population (fitted)	✓	12
	45-49	0·3	BC screening population (fitted)	✓	12
	50-54	0·1	BC screening population (fitted)	✓	12
	55-59	0·4	BC screening population (fitted)	✓	12
	60-64	0·1	BC screening population (fitted)	✓	12

	65-69	0·2	BC screening population (fitted)	✓	[12]
	70-74	0·2	US National probability sample (fitted)		[13]
	75-79	0·2	US National probability sample (fitted)		[13]
	80-84	0·2	US National probability sample (fitted)		[13]
	85-89	0·2	US National probability sample (fitted)		[13]
	90+	0·1	US National probability sample (fitted)		[13]
Progression Persistent Infection>CIN1	All	Calibrated	Placebo arm of HPV vaccine trial		[14]
Progression CIN1>CIN2	All	Calibrated	TOMBOLA trial		[15]
Progression CIN2>CIN3	All	Calibrated	Prospective Japanese cohort		[16]
Progression CIN3>Cancer	All	Calibrated	National Women's Hospital, Auckland, New Zealand		[17]
HPV31/33/45/52/58					
Median infection duration (months)	All	16·1	Placebo arm of HPV vaccine trial		[11]
Incidence rate (/100 year)	15-19	5·3	BC screening population	✓	[12]
	20-24	7·0	BC screening population	✓	[12]
	25-29	3·9	BC screening population	✓	[12]
	30-34	1·4	BC screening population	✓	[12]
	35-39	2·8	BC screening population	✓	[12]
	40-44	2·4	BC screening population	✓	[12]
	45-49	0·7	BC screening population	✓	[12]
	50-54	0·5	BC screening population	✓	[12]
	55-59	0·8	BC screening population	✓	[12]
	60+	0·0	BC screening population	✓	[12]
RR Progression infection>CIN1	All	Calibrated	Canadian CIN & cervical cancer cases	✓	[18]
RR Progression CIN1>CIN2	All	Calibrated	Canadian CIN & cervical cancer cases	✓	[18]
RR Progression CIN2>CIN3	All	Calibrated	Canadian CIN & cervical cancer cases	✓	[18]
RR Progression CIN3>Cancer	All	Calibrated	Canadian CIN & cervical cancer cases	✓	[18]
HPV35/39/51/56/59/66/68					
Median infection duration (months)	All	12·0	Placebo arm of HPV vaccine trial		[11]
Incidence rate (/100 year)	15-19	9·9	BC screening population	✓	[12]
	20-24	8·7	BC screening population	✓	[12]
	25-29	4·1	BC screening population	✓	[12]
	30-34	3·0	BC screening population	✓	[12]
	35-39	2·3	BC screening population	✓	[12]
	40-44	1·2	BC screening population	✓	[12]
	45-49	0·2	BC screening population	✓	[12]
	50-54	1·2	BC screening population	✓	[12]
	55-59	0·2	BC screening population	✓	[12]
	60-64	1·8	BC screening population	✓	[12]
	65-69	1·5	BC screening population	✓	[12]
	70-74	1·4	US National probability sample (fitted)		[13]
	75-79	1·4	US National probability sample (fitted)		[13]
	80-84	1·4	US National probability sample (fitted)		[13]
	85-89	1·3	US National probability sample (fitted)		[13]
	90+	1·2	US National probability sample (fitted)		[13]
RR Progression infection>CIN1	All	Calibrated	Canadian CIN & cervical cancer cases	✓	[18]
RR Progression CIN1>CIN2	All	Calibrated	Canadian CIN & cervical cancer cases	✓	[18]
RR Progression CIN2>CIN3	All	Calibrated	Canadian CIN & cervical cancer cases	✓	[18]
RR Progression CIN3>Cancer	All	Calibrated	Canadian CIN & cervical cancer cases	✓	[18]
Other HR HPV types					
Median infection duration (months)	All	12·0	Placebo arm of HPV vaccine trial		[11]
Incidence rate (/100 year)	15-19	5·0	BC screening population	✓	[12]
	20-24	3·5	BC screening population	✓	[12]
	25-29	1·9	BC screening population	✓	[12]
	30-34	1·6	BC screening population	✓	[12]
	35-39	0·7	BC screening population	✓	[12]
	40-44	0·6	BC screening population	✓	[12]
	45-49	0·4	BC screening population	✓	[12]
	50-54	1·1	BC screening population	✓	[12]
	55-59	0·6	BC screening population	✓	[12]
	60-64	1·5	BC screening population	✓	[12]
	65-69	1·3	BC screening population	✓	[12]
	70-74	1·3	US National probability sample (fitted)		[13]
	75-79	1·3	US National probability sample (fitted)		[13]
	80-84	1·2	US National probability sample (fitted)		[13]
	85-89	1·2	US National probability sample (fitted)		[13]
	90+	1·0	US National probability sample (fitted)		[13]
RR Progression infection>CIN1	All	Calibrated	Canadian CIN & cervical cancer cases	✓	[18]
RR Progression CIN1>CIN2	All	Calibrated	Canadian CIN & cervical cancer cases	✓	[18]

RR Progression CIN2>CIN3	All	Calibrated	Canadian CIN & cervical cancer cases	✓	18
RR Progression CIN3>Cancer	All	Calibrated	Canadian CIN & cervical cancer cases	✓	18
Screening					
Screening participation (per 42 months)	18-19	29·2%	CCHS 2012	✓	19
	20-29	61·5%	Cancer Quality Council of Ontario	✓	20
	30-39	67·7%	Cancer Quality Council of Ontario	✓	20
	40-49	67·3%	Cancer Quality Council of Ontario	✓	20
	50-59	64·3%	Cancer Quality Council of Ontario	✓	20
	60-69	53·2%	Cancer Quality Council of Ontario	✓	20
Screening participation (per 36 months)	70-74	37·9%	CCHS 2012	✓	19
	75-79	21·7%	CCHS 2012	✓	19
	80+	9·5%	CCHS 2012	✓	19
RR screening participation for women after hysterectomy	30-34	0·74	CCHS 2013-2014	✓	2
	35-39	0·64	CCHS 2013-2014	✓	2
	40-44	0·67	CCHS 2013-2014	✓	2
	45-49	0·41	CCHS 2013-2014	✓	2
	50-54	0·66	CCHS 2013-2014	✓	2
	55-59	0·54	CCHS 2013-2014	✓	2
	60-64	0·55	CCHS 2013-2014	✓	2
	65-69	0·49	CCHS 2013-2014	✓	2
	70+	0·58	CCHS 2013-2014	✓	2
Cytology sensitivity to CIN1	All	68·0%	Systematic Review		21
Cytology sensitivity to CIN2+	All	55·4%	Canadian Cervical Cancer Screening Trial	✓	22
Cytology specificity to <CIN2	All	96·8%	Canadian Cervical Cancer Screening Trial	✓	22
Loss to follow-up of <CIN2 screen-positives (per year)	<30	29·4%	Ontario Cervical Screening Program	✓	23
	30-39	23·4%	Ontario Cervical Screening Program	✓	23
	40-49	20·8%	Ontario Cervical Screening Program	✓	23
	50-59	22·5%	Ontario Cervical Screening Program	✓	23
	60+	22·7%	Ontario Cervical Screening Program	✓	23
Loss to follow-up of CIN2+ screen-positives (per year)	<30	21·0%	Ontario Cervical Screening Program	✓	23
	30-39	17·2%	Ontario Cervical Screening Program	✓	23
	40-49	18·4%	Ontario Cervical Screening Program	✓	23
	50-59	18·6%	Ontario Cervical Screening Program	✓	23
	60+	18·5%	Ontario Cervical Screening Program	✓	23
CIN treatments					
Probability CIN1 lesion is recommended for colposcopy+ treatment when screen-positive	18-19	2·6%	BC Cancer Agency	✓	5
	20-29	8·4%	BC Cancer Agency	✓	5
	30-39	8·2%	BC Cancer Agency	✓	5
	40-49	9·0%	BC Cancer Agency	✓	5
	50-59	9·1%	BC Cancer Agency	✓	5
	60-69	7·8%	BC Cancer Agency	✓	5
	70+	20·0%	BC Cancer Agency	✓	5
Probability CIN2+ lesion is recommended for colposcopy+ treatment when screen-positive	18-19	92·7%	BC Cancer Agency	✓	5
	20-29	97·3%	BC Cancer Agency	✓	5
	30-39	96·7%	BC Cancer Agency	✓	5
	40-49	84·2%	BC Cancer Agency	✓	5
	50-59	65·3%	BC Cancer Agency	✓	5
	60-69	64·8%	BC Cancer Agency	✓	5
	70+	28·1%	BC Cancer Agency	✓	5
Treatment failure probability (lesion remains)	All	14·0%	BC Cohort Study	✓	24
Treatment failure probability (persistent infection remains)	All	15·8%	Systematic review		25
Cancer symptoms & survival					
Probability preclincial cancer becomes symptomatic (per 0·5 year)	All	Calibrated	Assumption		-
Probability of dying of cancer for cervical cancer cases (per 0·5 year)	All	9·1%	Fitted to net 5-year cancer survival	✓	6
Probability of cancer remission (per 0·5 year)	<45	56·5%	Fitted to net 5-year cancer survival	✓	6
	45-54	24·8%	Fitted to net 5-year cancer survival	✓	6
	55-64	21·0%	Fitted to net 5-year cancer survival	✓	6
	65-74	12·4%	Fitted to net 5-year cancer survival	✓	6
	75+	2·0%	Fitted to net 5-year cancer survival	✓	6

BC=British Columbia; CCHS=Canadian Community Health Survey; CIN=cervical intraepithelial neoplasia; HPV=Human papillomavirus; HR=High risk; RR=risk ratio; US=United States.

2 MODEL CALIBRATION

2.1 Aim

The object of calibration was to find model parameter values able to reproduce empirical cervical cancer epidemiology before the impact of HPV vaccination. Due to the substantial uncertainty surrounding oncogenic progression and regression rates and the preclinical period of cervical cancer before development of symptoms, these parameters were selected for calibration. Plausible values for these parameters were sampled from distributions informed by epidemiological studies, and we identified the values that best reproduce Canadian data.

2.2 Empirical data to reproduce

In order to credibly inform cervical cancer screening practices, the model should be able to reproduce HPV infection prevalence by age, CIN prevalence, cervical cancer incidence by age, and HPV type distribution in cervical cancer. In Table A3 we present the data to which we fitted the model.

Table A3. Canadian epidemiological data used for model calibration

Data	Age (years)	Value	Assumed distribution	Data source	Ref.
HR HPV prevalence	15-19	25·7%	Binomial	BC screening population	12
	20-24	33·2%	Binomial	BC screening population	12
	25-29	21·9%	Binomial	BC screening population	12
	30-34	12·6%	Binomial	BC screening population	12
	35-39	9·5%	Binomial	BC screening population	12
	40-44	8·4%	Binomial	BC screening population	12
	45-49	4·2%	Binomial	BC screening population	12
	50-54	3·3%	Binomial	BC screening population	12
	55-59	3·0%	Binomial	BC screening population	12
	60-64	3·7%	Binomial	BC screening population	12
	65-69	0·8%	Binomial	BC screening population	12
CIN2+ prevalence (/1,000 women screened)	20-69	6·9	Normal	BC Cancer Agency, Canadian Partnership Against Cancer	5,26
Cervical cancer incidence rate (/100,000 women)	<20	0·0	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	20-24	1·1	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	25-29	6·3	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	30-34	10·7	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	35-39	14·2	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	40-44	15·8	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	45-49	12·8	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	50-54	10·4	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	55-59	10·8	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	60-64	10·1	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	65-69	9·6	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	70-74	8·6	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	75-79	8·2	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	80-84	10·5	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	85-89	5·3	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
	90+	5·0	Poisson	CANSIM Table 103-0550 (average 2011-2013)	27
HPV16/18 attributable cervical cancers	All	79·3%*	Binomial	Canadian cervical cancer cases	18

BC=British Columbia; CIN=cervical intraepithelial neoplasia; HPV=human papillomavirus;
*HPV-negative cancers were excluded from the denominator to obtain the attributable proportion of HPV16/18 cancers.

2.3 Parameter priors and posteriors

For the calibrated parameters, we sampled values from the prior distributions in Table A4, informed by the literature. For the sampling, we increased the min-max intervals and standard deviations by 1·5-2x multipliers to ensure adequate coverage of the parameter space.

Table A4. Calibrated parameter priors

Parameter	Priors			
	Mean	Interval*	Sampling distribution	Ref.
HPV16/18				
Progression Persistent Infection>CIN1	13·0/1000 months	8·4-19·9/1000 months	Log normal	14
Progression CIN1>CIN2	27·0% in 3 years	14·0-43·0% in 3 years	Logit normal	15

Progression CIN2>CIN3	50·6% in 5 years	18·6-91·1% in 5 years	Logit normal	[16]
Progression CIN3>Cancer (<30y)†	13·0% in 5 years	8·0-20·0% in 5 years	Logit normal	[17]
Progression CIN3>Cancer (≥60y)†	13·0% in 5 years	8·0-20·0% in 5 years	Logit normal	[17]
HPV31/33/45/52/58				
RR Progression Persistent Infection>CIN1	0·7	0·5-1·0	Log normal	[18]
RR Progression CIN1>CIN2	0·6	0·2-1·7	Log normal	[18]
RR Progression CIN2>CIN3	0·6	0·2-1·5	Log normal	[18]
RR Progression CIN3>Cancer	0·5	0·3-1·1	Log normal	[18]
HPV35/39/51/56/59/66/68 & Other HR HPV				
RR Progression Persistent Infection>CIN1	1·0	0·8-1·4	Log normal	[18]
RR Progression CIN1>CIN2	0·2	0·1-0·6	Log normal	[18]
RR Progression CIN2>CIN3	0·1	0·0-0·6	Log normal	[18]
RR Progression CIN3>Cancer	0·7	0·3-1·4	Log normal	[18]
All				
Regression CIN1>Persistent Infection	-	8·0-45·5% in 2 years	Uniform logit	[10]
Regression CIN2>Persistent Infection	-	6·2-34·8% in 2 years	Uniform logit	[10]
Regression CIN3>Persistent Infection	-	6·2-34·8% in 2 years	Uniform logit	[10]
Cancer preclinical period	5·5 years	2-15 years	Log normal	-

CIN=cervical intraepithelial neoplasia; HPV=human papillomavirus; RR=risk ratio.

* Intervals represent min-max in the case of uniform logit distributions and 95% confidence intervals in the case of normal/log-normal/logit normal distributions. Intervals in the table were increased by 1·5-2x multipliers during sampling.

† Progression risks applicable for ages <30y and ≥60y; progression risks from 30-59 were modeled as a linear increase from the lower to the higher risk.

Progression risks from CIN3 to cervical cancer were modeled as an increasing linear function over age. We sampled 2 probabilities of progression from CIN3 to cervical cancer for each parameter set; the age-specific probability of progression was modeled as a linear increase with age between the ages of 30-59 from the lower to the higher of the two probabilities.

Progression risks for non-HPV16/18 HPV types were sampled as risk ratios (RR) relative to the risk of progression of HPV-16/18. We applied the same RR to the risks of progression of HPV35/39/51/56/59/66/68 and other HR HPV types. These were informed by the relative type distributions across CIN and cancer cases.[18]

We sampled a duration for the cancer preclinical period which we then converted to the per turn probability of symptomatic cancer detection. As the duration of the preclinical period of cervical cancer unknown, we assumed a 95% confidence interval of 2-15 years, based on the differences in peak ages of CIN3 and cervical cancer.

2.4 Calibration procedures

We sampled 40,000 parameter sets from the prior distributions in Table 3 using Latin Hypercube sampling.[28] We ran the model with these 40,000 parameter sets to obtain model-predicted HPV prevalences, CIN2+ prevalences, cervical cancer incidence rates, and HPV16/18 distributions in cervical cancers. For each parameter set, we calculated the log-likelihood that the empirical data in Table 2 was generated by that parameter set. We then resampled 3,000 parameter sets with replacement according their calculated log-likelihood. In this resample there were 55 unique parameter sets reproducing the empirical data. We used these final 55 unique parameter sets to perform model simulations. Model outputs are averaged over the 55 parameter sets, weighted according to the number of times they occurred in the 3,000 parameter set resample.

3 MODEL VALIDATION

We assessed the validity of the model by comparing the predictions of the 55 parameter sets to the empirical data used to select the parameter sets (Fit to calibration targets) and whether they could also reproduce other epidemiological data that had not been used to select the parameter sets (Fit to external validation targets). The

model predictions below use these 55 parameter sets; the average of the parameter sets is weighted according to their resample weights in the 3,000 resample.

3.1 Fit to calibration targets

The model provides a good overall fit to Canadian HR HPV prevalence (Figure 8), CIN2+ prevalence (Figure 9), cervical cancer incidence rates (Figure 10), and cancer HPV type distribution (Figure 11). However it underestimates the cervical cancer incidence rates in Canadian women aged 75-84 years (Figure 10). It is probable that the higher cancer incidence in women 75-84 years is due to a cohort effect in empirical data that the model is unable to reproduce; women in older cohorts have not had the same screening patterns throughout their lives as those measured in 2012, and have a higher underlying risk of cervical cancer than younger cohorts.[29] We calibrated the model assuming a common underlying risk of cervical cancer for all cohorts and constant age-specific screening participation rates over time, and therefore predict a lower cervical cancer incidence at older ages. Model results at older ages should therefore be interpreted as the predicted cervical cancer incidence if current screening participation trends by age continue.

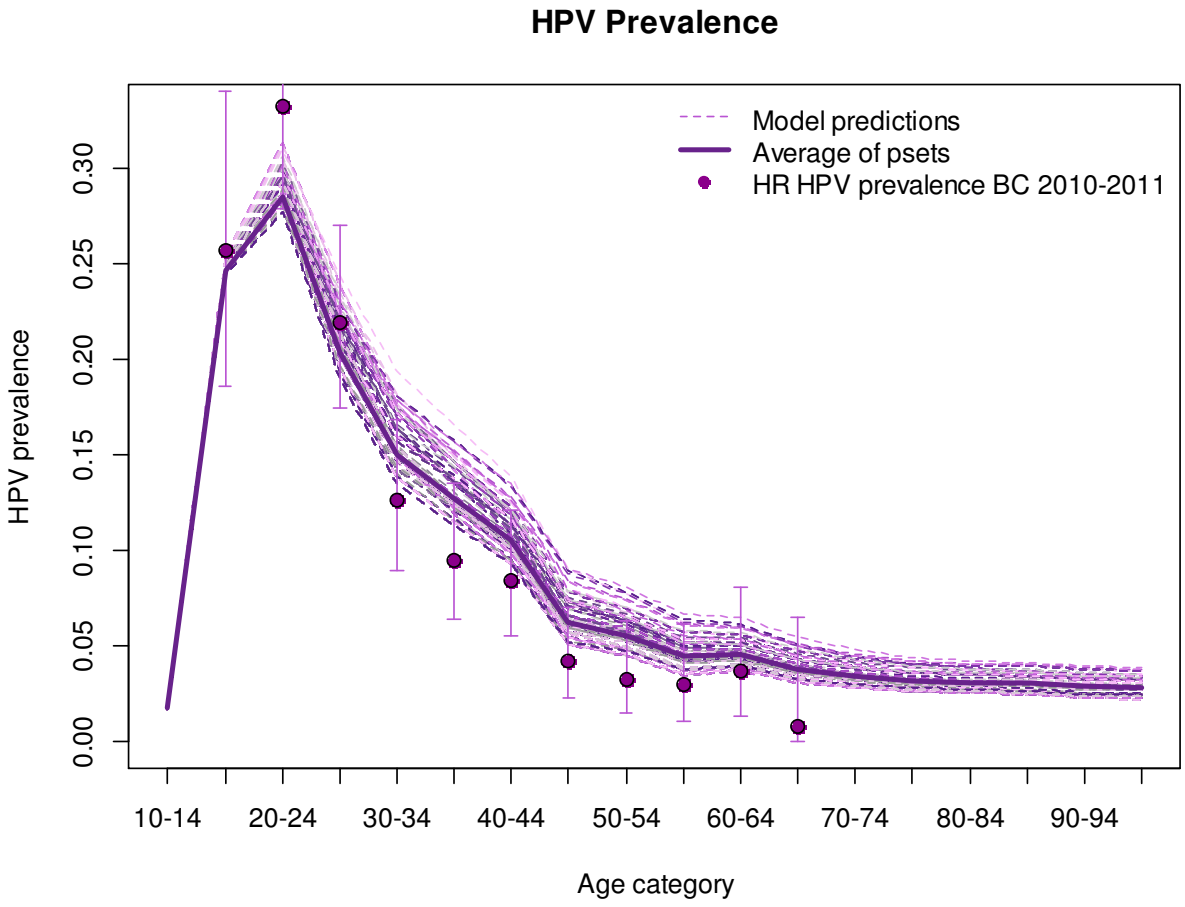

Figure 8. HR HPV prevalence.
Model predictions are compared to HR Hybrid Capture 2 positivity in a population-based sample of the British Columbia screening population (Ogilvie *et al.*).[12]

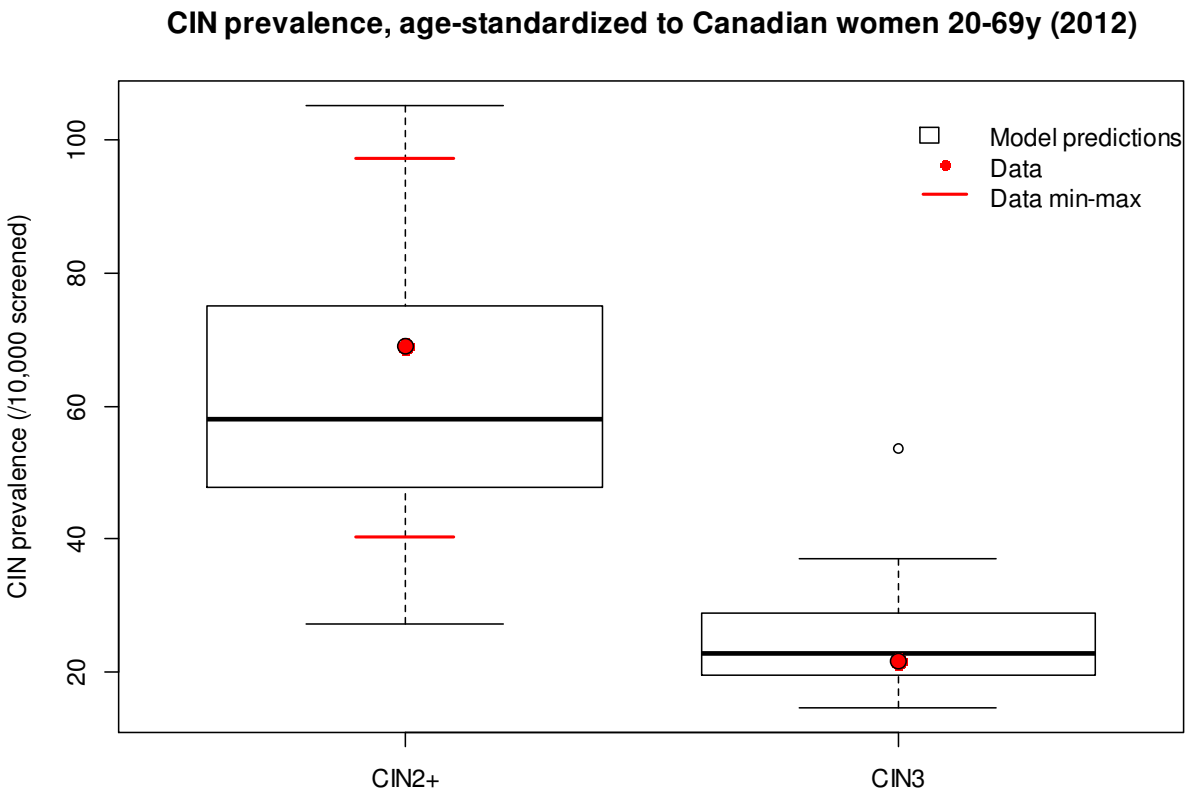

Figure 9. CIN2+ and CIN3 prevalence per 10,000 women screened.
Model prediction were age-standardized to the Canadian female population 20-69 years old and compared to the CIN2+ prevalence in British Columbia[5] and the CIN3/AIS prevalence in Ontario.[23] Min-max values were obtained by age-standardizing the minimum and maximum age-specific provincial CIN2+ prevalences reported by the Canadian Partnership Against Cancer (2016).[26] CIN=cervical intraepithelial neoplasia.

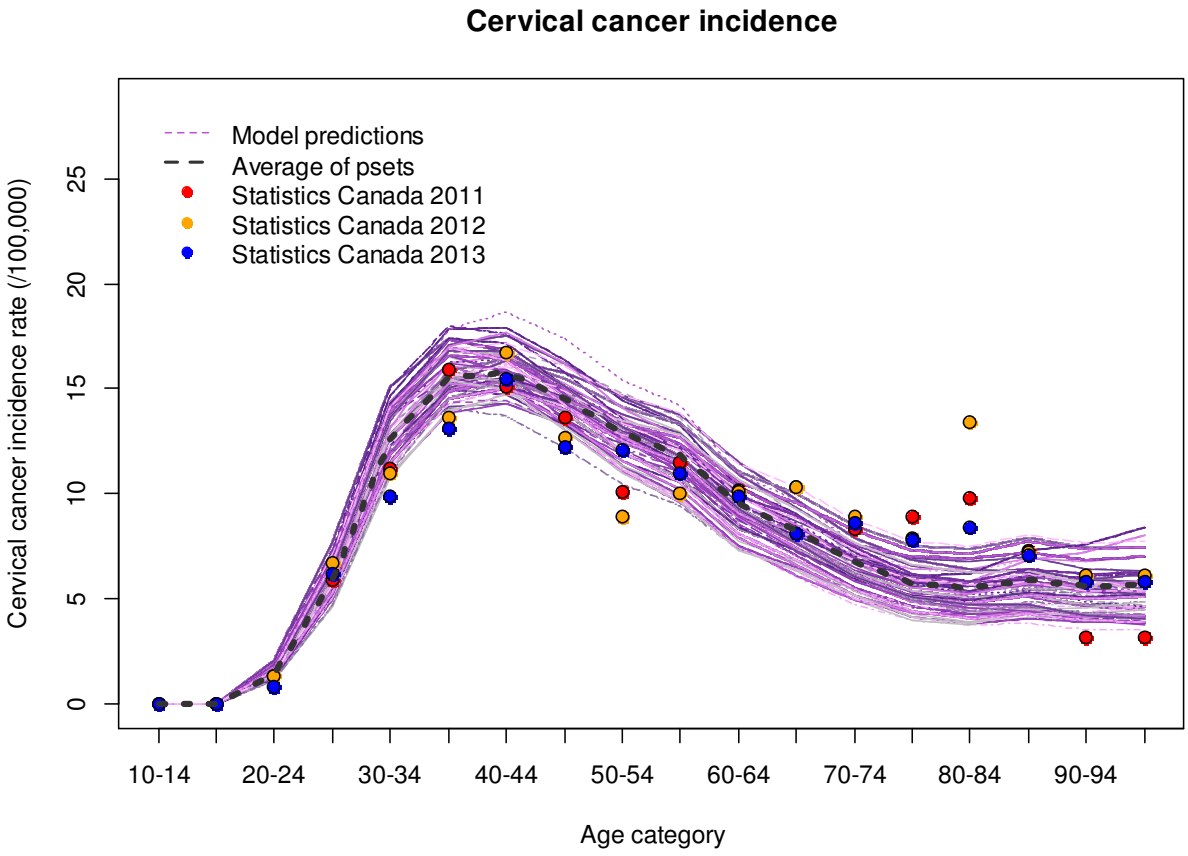

Figure 10. Cervical cancer incidence rates.
Each line represents one of 55 unique parameter sets. Model predictions are compared to 2011-2013 data from CANSIM Table 103-0550.[27]

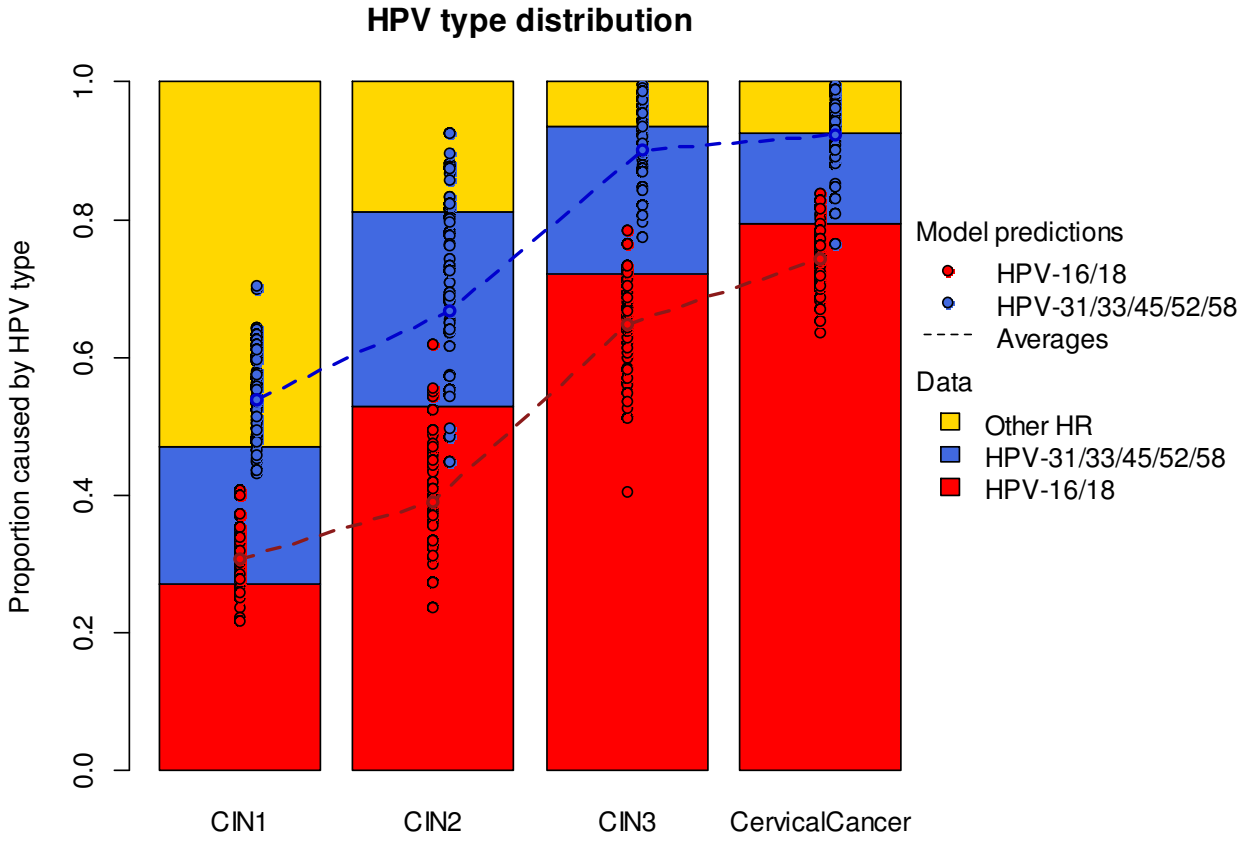

Figure 11. HPV type distribution in CIN and cervical cancer.
Each dot represents one of 55 unique parameter sets. Model predictions are compared to the type distribution in a sample of Canadian CIN and cervical cancer cases (Coutlée *et al.* 2011).[18] HPV type distributions have been redistributed over HPV-positive CIN and cervical cancer.

3.2 Fit to external validation targets

3.2.1 HPV prevalence

While there is no Canadian population-level data on the HR HPV prevalence under 15 years and over 69 years, data from a Scottish survey of adolescents suggests there should be a very low prevalence of HR HPV under 15 years (0·9%),[9] and data from a national representative sample of US women suggests a continued low prevalence of HR HPV in women 65-85 years (5·0-6·8%).[13] Model HR HPV prevalences reproduce these estimates (Figure 8). The model also reproduces Canadian HPV16/18 (Figure 12) and HPV31/33/45/52/58 (Figure 13) prevalences in a population-based sample of women attending screening.[12]

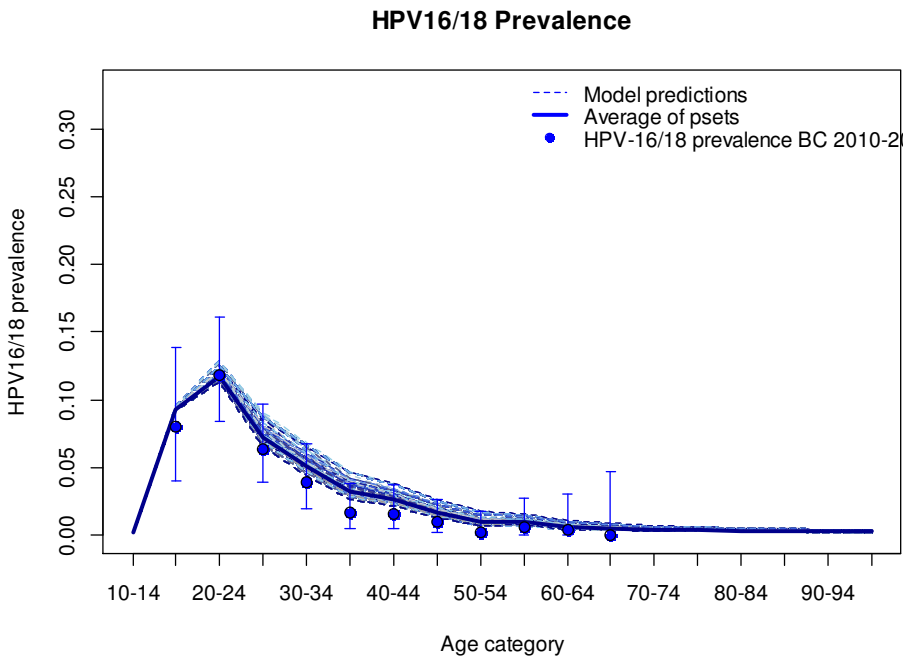

Figure 12. HPV16/18 prevalence by age.
Model predictions are compared to Roche Linear Array positivity in a population-based sample of the British Columbia screening population (Ogilvie *et al.*).[12]

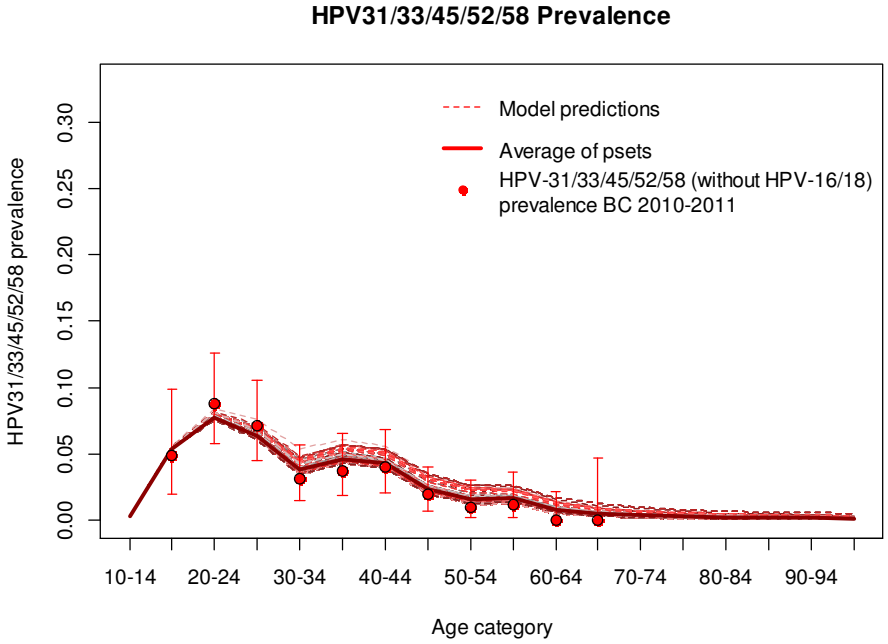

Figure 13. HPV31/33/45/52/58 prevalence by age.
Model predictions are compared to Roche Linear Array positivity for infection with HPV31/33/35/52/58 (excluding co-infections with HPV16/18) in a population-based sample of the British Columbia screening population (Ogilvie *et al.*).[12]

3.2.2 Screening outcomes

In 2012, 5·5% of screen-eligible Ontarian women who had a Pap test had an abnormal test result (>=ASCUS).[23] The model predicts similar positive screen test rates (Figure 14).

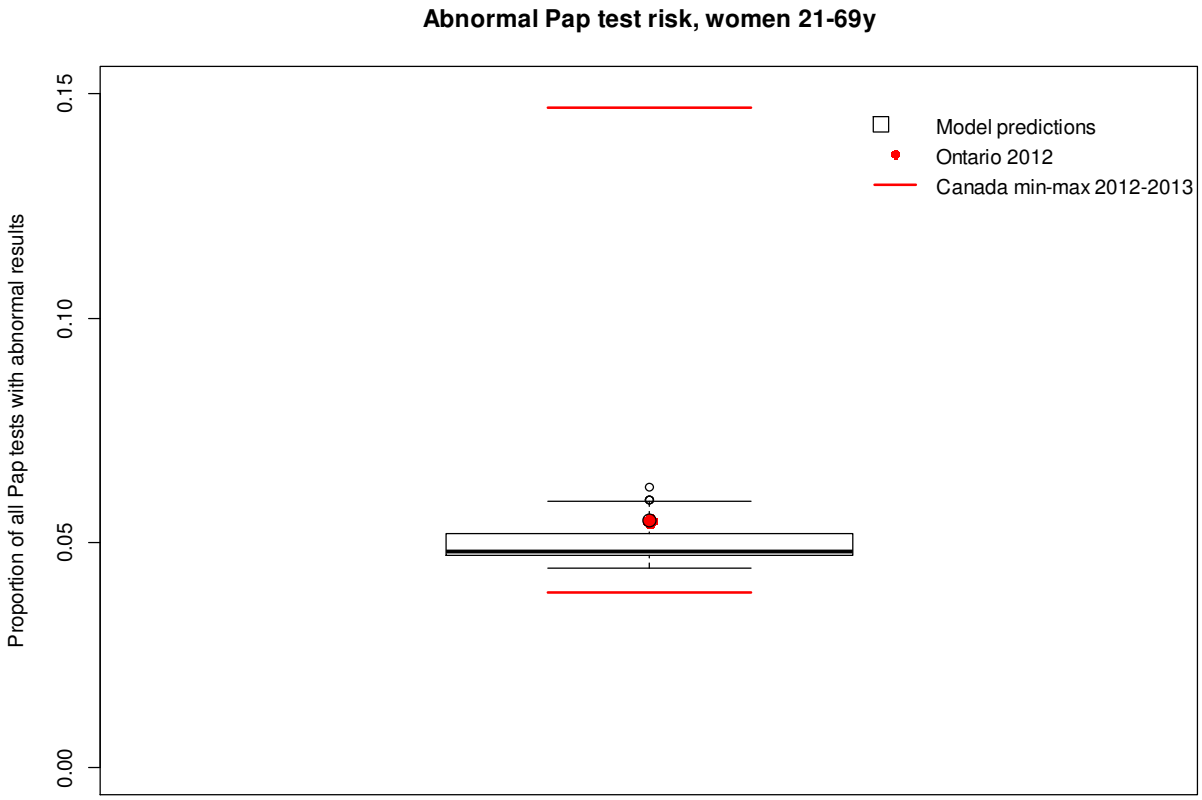

Figure 14. Proportion of screening tests that have abnormal results.
Model predictions are age-standardized and compared to the Ontario proportion of screen-eligible women who have had an abnormal Pap test result (>=ASCUS) in 2012.[23] The min-max interval corresponds to the minimum and maximum across Canadian provincial registries.[26]

3.2.3 Cumulative lifetime risk

In 2010, it was estimated that 1 in 152 Canadian women would develop cervical cancer over her lifetime and that 1 in 475 Canadian women would die of cervical cancer.[6] The model reproduces these cumulative lifetime risks (Figure 15, Figure 16).

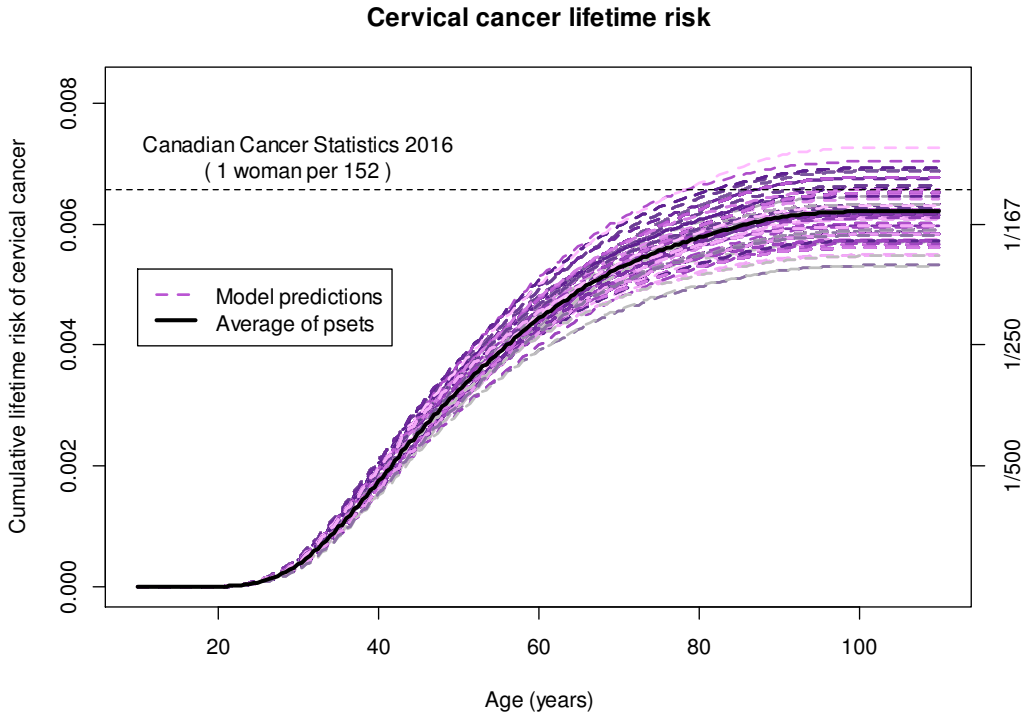

Figure 15. Cumulative cervical cancer risk by age.
Model predictions are compared to the estimated lifetime probability of developing cervical cancer in Canada in 2010.[6]

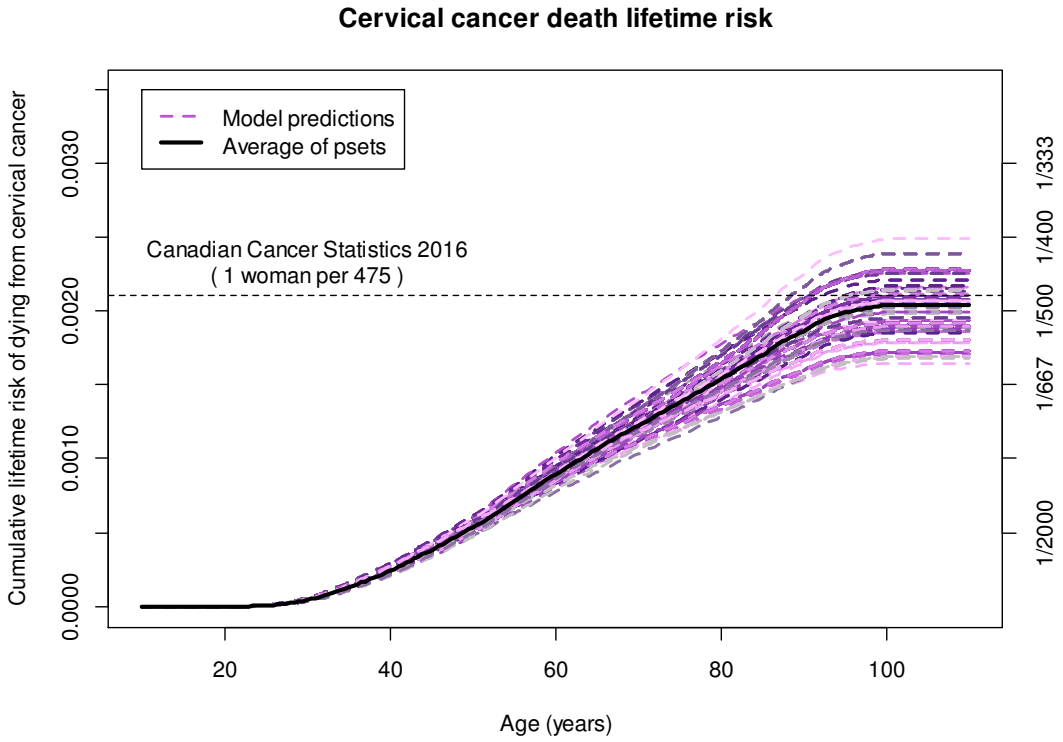

Figure 16. Cumulative cervical cancer death risk by age.
Model predictions are compared to the estimated lifetime probability of dying of cervical cancer in Canada in 2010.[6]

3.2.4 Impact of screening on cervical cancer incidence

Because we compare screening strategies to strategies without screening, we need to ensure the model's natural history of cancer without screening is valid. The incidence of cervical cancer that would occur without screening is unknown, as population-level incidence rates have been influenced by decades of screening. The only way to validate model predictions without screening is to compare the predicted incidence rate to historical cervical cancer incidence rates before the wide scale implementation of screening. This method is imperfect as the background risk of cervical cancer without screening may have been different in the mid-20th century due to other cohort and time effects (sexual behaviors, hysterectomy rates, fertility rates). However, if model predictions can roughly reproduce historical rates, it increases the reassurance that the model can validly reproduce the natural history of cervical cancer in absence of screening.

The earliest published cervical cancer incidence rates we are aware of are for British Columbia from 1955-1957[30] and for Alberta, Saskatchewan, Manitoba, Newfoundland, and Québec from 1963-1966.[31] Cytological screening first started in British Columbia in 1949; however screening efforts were slow to scale up and only approximately 3% of the province's population had been screened by 1955.[30] Screening coverage in the other provinces took longer to increase; across Canada the coverage was only 6% by 1962 but had increased to approximately 22% by 1967.[32] Therefore, while screening had already started in Canada between 1955 and 1966, it would likely not yet have substantially reduced cervical cancer rates due to its low coverage and because preventive benefits would not yet have had time to accrue. It is however possible that data from these time periods would have a slightly inflated cervical cancer incidence at younger ages due to some early detection of preclinical cancers when a screening program begins.

The model predicts that, if there was no screening for cervical cancer, current rates of cervical cancer would be very similar to those observed in various Canadian provinces between 1955 and 1966 (Figure 17).

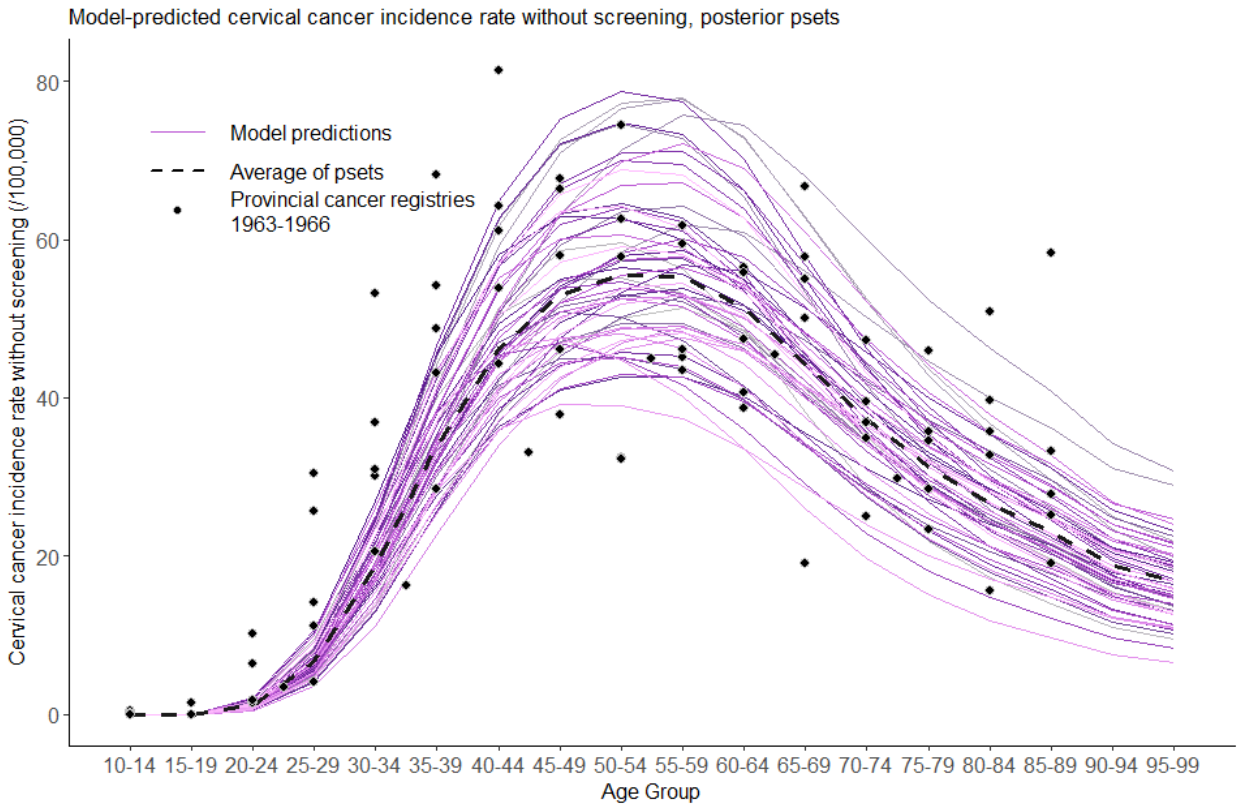

Figure 17. Cervical cancer incidence rate predicted without screening.
Model predictions are compared to cervical cancer incidence rates from provincial cancer registries from 1963-1966[31] and the 1955-1957 incidence rates from BC.[30] Black points correspond to data from individual registries.

4 DETAILED PARAMETER CALCULATION NOTES

4.1 Transformation of rates and risks

Yearly rates (λ) and risks (r_t) in the model were transformed into 0·5 year risks ($r_{0.5}$) using the following formulas:

$$r_{0\cdot5} = (1 - r_t)^{\frac{1}{t}*0\cdot5}$$

$$r_{0\cdot5} = 1 - e^{-\lambda*0\cdot5}$$

4.2 Background death rates

We removed cervical cancer deaths from the background death rates in order to avoid double counting.

4.3 Hysterectomy risk

We estimated 5-year hysterectomy risks by taking the difference in the prevalence of hysterectomy between adjacent age groups. We smoothed the hysterectomy risks over age by averaging the risk differences with the next youngest and oldest age group (see Figure 2).

4.4 Infection duration & clearance rates

Median infection durations ($d_{0.5}$) were transformed into infection clearance probabilities per 0·5 months ($c_{0.5}$):

$$c_{0\cdot5} = 1 - e^{\frac{\ln(0\cdot5)}{d_{0\cdot5} \div 12\ months}*0\cdot5}$$

4.5 HPV infection rates

HPV infection rates are meant to represent the combined incidence of both new infections and the reactivation of latent infections, as these are indistinguishable in empirical data. There is no data to inform HPV infection prevalence in 10-14 year-olds and age groups above 69 years in Canada, so we supplemented with data from a sample of Scottish schoolchildren[9] and a national probability sample of community women from the United States[13] for these age groups.

We assumed HPV prevalences in Canada before vaccination were in a state of equilibrium (inflow=outflow), and derived incidence rates from the classic formula:

$$Incidence = \frac{Prevalence * Duration^{-1}}{1 - Prevalence}$$

In an age-stratified population, it is necessary to account for inflow from those aging into an age group and the outflow from those clearing the infection and aging out of the age group. Age-specific HPV incidence rates were derived from HPV prevalence data using the following formula:

$$HPVincidence_{a,t} = \frac{HPVprevalence_{a,t}(c_t) - HPVprevalence_{a-1,t}\left(\frac{1}{N_a}\right) + HPVprevalence_{a+1,t}\left(\frac{(1-\mu_a)^5}{N_a}\right)}{1 - HPVprevalence_a}$$

Where:

- $HPVincidence_{a,t}$=The incidence rate of infection with HPV type *t* in age group *a*
- $HPVprevalence_{a,t}$=The prevalence of infection with HPV type *t* in age group *a*
- c_t=The clearance rate of HPV type *t*
- μ_a=The mortality rate in age group *a*
- N_a=The size of the age group calculated with the integral $\int_0^5 (1-\mu_a)^t dt$
  - This quantity allows determining the proportion of women aging into $\left(\frac{1}{N_a}\right)$ and out of $\left(\frac{(1-\mu_a)^5}{N_a}\right)$ the age group relative to the total size of the age group.

For parameter calculations and for model calibration, we used HPV31/33/45/52/58 prevalence excluding coinfections with HPV16/18, and we used HPV35/39/51/56/59/66/68 & other HR prevalences excluding coinfections with HPV16/18/31/33/45/52/58.

4.6 Cancer symptomatic detection probability

Preclincial cancer durations (p) were transformed into rates of symptom development (p^{-1}), which were then transformed into the probability a preclinical cancer becomes sypmtomatic per 0·5 years ($1 - e^{-p^{-1}*0.5}$)

4.7 Probability of dying of cancer & cancer remission

The probability of dying of cervical cancer and of cervical cancer remission were fitted to reproduce age-specific net cervical cancer 5-year survival in Canada[6] (the observed survival in cancer cases relative to the expected age-specific survival in a population without cervical cancer):

Table A5. Age-specific net 5-year cervical cancer survival.[6]

Age group (years)	Net 5-year survival
15-44	85%
45-54	72%
55-64	69%
65-74	60%
75-99	43%

We tested several model parameter structures and found that cervical cancer mortality rates in Canada were best reproduced with age-specific remission rates. We therefore assumed all age groups had the same risk of dying of cancer per time step, and used the Excel Solver tool to find a risk dying of cancer per 0·5 years while living with cancer (9·1%) and the age-specific probabilities of cancer remission which reproduced the above net 5-year survivals. Therefore, while cancer cases in all age groups have a high probability of dying of cancer within the first year of diagnosis, the net 5-year survival is substantially better in younger age groups than older age groups due to the higher remission rate.

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