ACCEPTED MANUSCRIPT

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

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ABSTRACT

Background: There is limited empirical evidence to inform the age at which to stop cervical cancer screening. We used a Markov model of cervical cancer screening to estimate remaining lifetime risks at different ages and with different exit screening tests.

Methods: We calibrated our model to human papillomavirus infection and cancer incidence. We estimated 5-year, 10-year and remaining lifetime risks of cervical cancer for older unvaccinated women who stop screening at different ages with different screening tests, excluding women who have undergone hysterectomies.

Findings: Crude incidence rates may underestimate the incidence of cervical cancers in at-risk older women by up to 71% if women with hysterectomies are not excluded from the denominator. The model predicted that a woman who never screens would have a 1/45 lifetime risk of cervical cancer; regular screening between the ages of 25-69 would reduce her lifetime risk to 1/532. Increasing the age at which a woman stops cytology screening from 55 to 75 led to incremental decreases in her cancer risk later in life. A 70-year old woman whose screening history is unknown had an average remaining lifetime risk of 1/588 if she stopped screening. Her remaining lifetime risk at age 70 was reduced to 1/1206 (2·0-fold reduction) if she had a negative cytology test, 1/6525 (12·9-fold reduction) if she had a negative HPV test, and 1/9550 (18·1-fold reduction) if she had a negative co-test.

Interpretation: Later life reductions in cervical cancer risk may be achieved by screening up to age 75 with cytology, though with diminishing returns. An exit HPV test or co-test may provide reassurance of a very low remaining lifetime cervical cancer risk for unvaccinated women with a cervix past the age of 55.

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RESEARCH IN CONTEXT

Evidence before this study

The American Society of Clinical Oncology (ASCO) Expert Panel had previously performed 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, Chochrane, and National Guideline Clearinghouse databases 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 panel, and additionally the guidelines published by the Canadian Task Force on Preventive Health Care (CTFPHC) and the US Preventive Service Task Force (USPSTF), in order to identify the evidence policy makers used worldwide to inform recommendations on the age at which to stop cervical cancer screening. Though most current guidelines recommend cervical cancer screening may stop after the age of 65 or 69 in high-income settings, most also note the low-quality evidence this recommendation is based on. Many guidelines do not mention women with hysterectomies; some guidelines specify women who have had a total hysterectomy should no longer be screened, but do not use cervical cancer incidence rates which exclude hysterectomies from the denominator when assessing the value of screening at older ages. Two guidelines referred to a modeling analysis as a source of evidence for their recommendations for the age at which to stop screening due to the limited empirical evidence.

Added value of this study

This study uses a model of cervical cancer natural history calibrated to data to simulate the remaining lifetime risk of cervical cancer to address the limited empirical evidence for screening in older women. We project 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 currently very challenging to do with registry data or in an empirical study. We find that there may be prevention of cervical cancers in later life with cytology screening up to age 75, which may have been underestimated by policy-makers because registry data generally does not remove women with hysterectomies from denominators. However, there is very limited benefit in screening in women with a negative HPV test past the age of 55, a conclusion that holds true whether hysterectomy rates are taken into account or not.

Implications of all the available evidence

There are preventive benefits of screening women with a cervix using cytology up to approximately age 75, though 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 past the age of 55 were predicted to be at very low risk of cervical cancer for the rest of their lives.

INTRODUCTION

Human papillomavirus (HPV) vaccination promises 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 current recommended age to stop cervical cancer screening generally varies between 50-70 years old worldwide.[1] However, agencies making screening recommendations have recognized that these recommendations are based on low-quality evidence on the effectiveness of screening in older women.[2-4] Cervical cancer incidence and mortality rates remain high in older women; for example, US women ≥70 years old have higher cervical cancer mortality rates (5·3-6·5/100,000) than women 40-44 years old (3·2/100,000)[5]. There is some evidence that women ≥65 years old who screen have lower cervical cancer incidence than women ≥65 years old who do not screen,[6,7] but it is unclear whether this reduction is only a residual protective effect from having also been screened at younger ages. 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 removing the cervix are no longer at risk for cervical cancer and need no longer be screened.[2-4] Age-specific cancer incidence rates from national cancer registries generally do not exclude women with hysterectomies from their denominators, and as a result cervical cancer incidence rates may be substantially underestimated in older women with a cervix.[10-12] This may lead to underestimating the benefits of screening in older women by policy makers, who depend on this same registry data to determine cancer risk in older women.

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

Due to an aging world population, we may be confronted with increasing numbers of cervical cancers diagnosed at older ages, and an increased demand for the prevention of diseases in these age groups.[14] In this study, our objective was to model the remaining lifetime risks of cervical cancer for women with a cervix who stop screening at different ages and with different tests, in order to inform recommendations of the age at which to stop cervical cancer screening.

METHODS

Study design and data sources

We developed a state-transition (Markov) model of cervical cancer natural history and screening using the R version 3.3.0 language and programming environment. In order to ground our analyses in an empirical context, we calibrated and validated our model using Canadian provincial registries and survey data. A detailed description of the model's structure, parameters, and development is provided in the Supplementary Appendix (p.3). This research uses aggregate secondary data sources, and thus did not require Institutional Review Board approval.

Model description

Demographics. The model represents the female population aged 10-100 years old. Women are subject to background age-specific mortality rates. Successive cohorts enter the model at age 10, creating an age-structured population. For this analysis, we did not model the impact of HPV vaccination as we focused on older birth cohorts. We assumed a background age-specific rate of total hysterectomies for unrelated health reasons. Once a woman has had a total hysterectomy, she is assumed to be no longer at risk for cervical cancer. In the model, 42% of women who live until the age of 100 will have had a total hysterectomy, based on a Canadian population health survey.[15]

Natural history of cervical cancer (Figure 1). Uninfected women acquire transient HPV infections at an age-specific rate, which may eventually become persistent infections. Persistent HPV infections may progress sequentially to cervical intraepithelial neoplasia (CIN) 1-3. All CIN states may regress to a persistent HPV infection. Women with CIN3 may progress to cervical cancer at an age-specific rate. We opted for a 3-stage progressive CIN model in order to include differences in management and treatment decisions depending on lesion severity. We model infections with four high risk (HR) HPV groups: HPV16/18, HPV31/33/45/52/58, HPV35/39/51/56/59/66/68, and a generic group of other potentially oncogenic HPV. Infection incidence rates, clearance rates, and oncogenic progression rates are group type-specific. Women infected 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 HPV.

Screening & treatment. All women 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 her underlying health state. Sensitivity and specificity are assumed independent of previous test results. Currently, we model the sensitivity and specificity of cytology.[16] Screen-positive women have a probability of having their underlying lesion treated; those who are not treated are retested with cytology every year. The probability of getting treated is higher for high grade lesions than for low grade lesions. Women have a probability of being lost to follow-up. If lost to follow-up, she does not attend scheduled treatments and follow-up; she returns to the general screening population. Cervical cancers have a probability of developing symptoms and being detected outside of screening. Women with detected cervical cancer have an excess cervical cancer mortality rate, a background mortality rate from other causes, and a remission rate. Remission is defined as 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.

Parameter values & calibration. For a full list of parameter values, see the Supplementary Appendix (p.8). We calibrated the oncogenic progression and regression rates 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] Using Latin Hypercube sampling, we sampled 40,000 combinations of values for the oncogenic progression and regression rates and the preclinical period of cervical cancer. We ran the model with these 40,000 parameter sets, and calculated the log-likelihood that the empirical data was generated by that parameter set. We used these log-likelihoods to resample 3,000 parameter sets with replacement. In this resample there were 55 unique parameter sets reproducing the HPV prevalence, screening outcomes, cervical cancer incidence, mortality, and cumulative lifetime risk in Canada (see Supplementary Appendix p.13).

Statistical Analysis

Our base case scenario reflects actual average cervical cancer screening adherence, with 53-68% of women aged 20-69 being screened at least once in the past 42 months, depending on age.[18] Some women continue screening after the age of 69 years, but the proportion declines with age. This base case scenario is meant to represent a realistic assessment of risk for a typical woman, considering average screening attendance. We compare this base case to scenarios of: 1) no screening 2) perfect screening adherence (100% of women screened once every 3 years between the ages of 25-69, no screening in other age groups), 3) if women with typical screening adherence stopped screening at different 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 North American and European clinical trials and meta-analyses correcting for verification bias.[16,21-23] HPV testing is assumed to have 100% sensitivity to detect HPV-16/18/31/33/35/39/45/51/52/56/58/59/66/68; its sensitivity to CIN therefore varies between parameter sets depending on HPV type distribution in CIN and is on average 91/97% for CIN2/3.

We calculated cervical cancer incidence rates both including and excluding women with 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.

We performed sensitivity analyses varying the rate of hysterectomies, the sensitivity of cytology (40 and 70%), doubling the prevalence of HPV in women aged 55 and above, and restricting analyses to women with no current underlying CIN or cancer (true normals). These sensitivity analyses were done to examine the potential impacts of variations in hysterectomy rates and cytology sensitivity across contexts, potential future increases in HPV prevalence in older age groups, and approximate the risk after a long history of negative cytology screening.

Model predictions were averaged over the selected 55 parameter sets and weighted according to the number of times they occurred in the 3,000 parameter set resample. The variability across parameter set estimates is reported using the minimum and maximum predictions from the 55 parameter sets, presented as error bars or between brackets [].

Role of the funding source

The funder played no role in the writing of the manuscript, the collection/analysis of the data, or the decision to submit it for publication. 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

Cervical cancer incidence rates including & excluding hysterectomies

We first modeled cancer incidence with typical cytology screening adherence and hysterectomy rates to evaluate the current underestimation of cervical cancer rates in at-risk women due to hysterectomies. The model suggests that the incidence rate of cervical cancer in women with a cervix is likely considerably underestimated in women ≥40 years old when hysterectomies are not excluded from the denominator (Figure 2, grey lines). Cervical cancer incidence rates which do not exclude women with

hysterecomies from the denominator underestimated the incidence rate in women with a cervix by up to 71% in women aged 80-84.

Impact of a lifetime of cytology screening in cohorts who are not vaccinated

Estimates of cumulative lifetime risk (Figure 3) are meant to represent the risk from birth and therefore do not exclude hysterectomies (the denominator is the total size of the cohort at 10 years old). The cumulative lifetime risk of cervical cancer is predicted to be much higher for a woman who will never screen than for a woman with typical screening adherence, starting from age 30. We estimate that without screening or vaccination, 1/45 [minimum-maximum 1/30-71] women would be diagnosed with cervical cancer in her lifetime. A woman with typical screening adherence with cytology who stops screening at age 55 was predicted to reduce her lifetime risk to 1/138 [104-197], while a woman with typical screening adherence who stops screening at age 70 with cytology reduced her lifetime risk to 1/160 [119-225]. This suggests a substantial part of the reduction in the cumulative lifetime risk at older ages is due to screening before the age of 55 (compared to no screening). We estimate that perfect adherence to cytology screening every 3 years from age 25-69 would reduce the lifetime risk of cervical cancer to 1/532 [1/355-892] women without HPV vaccination. We observed similar impacts of screening when we estimated 10-year risks in women who have a cervix at the start of each 10 years (Figure 4).

Impact of recommended age to stop cervical cancer screening

Regardless of screening test results

First we predicted the impact if all women stopped cytology screening at a given age, assuming no differences in screening practice up to that age (Figure 2, Figure 5A). All scenarios lead to a temporary decrease in the incidence rate of cervical cancer in the 5 years following the age at which screening stopped, because screening would no longer detect preclinical cervical cancers. This temporary decrease was then followed by a later life increase in the rates of cervical cancers due to the later symptomatic detection of latent cancers and the lack of prevention of new cancers. Each 5-year delay in the age at which to stop screening up until age 75 led to incremental reductions in later cervical cancer incidence. A woman with a cervix who stops cytology screening at age 55 is predicted, once she reaches ages 70-85, to have approximately double the 5-year risk of cervical cancer compared to a woman who would have continued screening with typical screening adherence.

After a negative screening test

We estimated 5-year and remaining lifetime risks of cervical cancer for a woman with a cervix who stops 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 1). The model predicted that a woman with a cervix who tests HPV DNA negative to 14 HR HPV types and stops screening at 55 would have a remaining lifetime cervical cancer risk of 1/1,940, which is much lower than the remaining lifetime risk for a woman with a cervix who tests cytology negative (1/440) at the same age. The absolute risk for a woman with a negative co-test was similar to those for a woman with only a negative HPV test. Though 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. A woman who stops screening after a negative HPV test at age 55 was predicted to have a lower remaining lifetime risk of cervical cancer (1/1,940) than a woman with the same typical screening adherence but who continues cytology screening up to age 70 and then stops after a negative cytology test (1/1,206). Though a woman who has never screened before was predicted to be at higher risk of cervical cancer for the rest of her life compared to a woman with typical screening

adherence, a single negative HPV test still indicated a relatively low remaining risk of cervical cancer past the age of 55 (1/1,096) (Table 1).

A woman with a cervix at age 70 who stops screening had an average remaining lifetime cervical cancer risk of 1/588 [453-897] without an exit screen test. Compared to no exit screen test, a woman with a cervix at age 70 would have an average remaining lifetime risk that is 1/2·0 [2·0-2·1] times lower after a negative cytology test, 1/12·9 [5·3-40·5] times lower after a negative HPV test, and 1/18·1 [8·3-44·0] times lower after a negative co-test (Table 1). The absolute remaining lifetime risk of cervical cancer after a negative co-test was similar to the risk predicted for a true normal woman.

Sensitivity analyses

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 rate of hysterectomies did not substantially modify 10-year cervical cancer risks for women with a cervix and only slightly increased the remaining lifetime risks after age 55 (Figure 4, Supplementary Appendix p.2). The absolute remaining lifetime risk of cervical cancer increased when we assumed a 2-times higher prevalence of HR HPV in women aged 55 and over; however, the relative risk after an exit screen test remains similar. (Supplementary Appendix p.2). This suggests potential increases in HPV prevalence in older age groups due to 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 cotest was not substantially affected by the sensitivity of prior cytology screening up to that age (Supplementary Appendix p.2).

DISCUSSION

It has been debated whether reductions in cervical cancer incidence at older ages are due to the cumulative prevention from screening at younger ages or whether screening at older ages provides additional benefits.[6-9] In this study, we used a model of cervical cancer natural history in order to address the lack of empirical evidence for screening in older women. Our results suggests most of the prevention of cervical cancer in later life come from screening before the age of 55, but that continued cytology screening up to around age 75 can still lead to incremental decreases in cancer risk in later life. On the other hand, a woman who has a negative HR HPV test or co-test past the age of 55 years was predicted to be at a very low risk of cervical cancer for the rest of her life, lower than an woman who continues cytology screening with typical adherence rates.

Models of cervical cancer natural history such as ours are useful for policy decision analyses when long-term empirical evidence is challenging to acquire and thus help estimate the long-term health impacts of intervention. The US Preventive Services Task Force previously used a modeling framework to support its latest cervical cancer screening recommendations, notably due to the lack of empirical evidence in older women.[24] This other modeling analysis similarly found that the small incremental gains in life expectancy from cytology screening were expected to start tapering off between the ages of 65 and 75.[24] Some screening past the age of 65 might still however be cost-effective in a cytology screening context.[25]

Our risks were calibrated to be applicable to current generations of older women in developed countries with longstanding screening programs, who up until recently have lived most of their lives in a cytology screening context and are 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 rates between countries and over time.[12] The absolute risk of cervical cancer after an exit cytology screen depended on the assumed cytology test sensitivity in our analyses. The risk after a negative exit HPV test or cotest was however little affected by the sensitivity of prior cytology screening up to the age of the exit screen. This suggests that while the absolute risk of cervical cancer at older ages may 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 may not be applicable to future cohorts with high vaccination coverage or who will have been screened most of their lives with HPV testing. However, as it will still take many decades before cohorts vaccinated as adolescents reach the ages of 50-70, our results are likely to be applicable to older cohorts of women for many years to come.

Cervical cancer incidence rates from registries often do not exclude women with hysterectomies from denominators(e.g. [5,19]). Registry cervical cancer incidence rates which include women with hysterectomies in the denominator are likely influenced by worldwide variations in age at which screening stops and the prevalence of hysterectomy.[12] For example, the model-predicted cancer incidence when cytology screening stops at age 60 (Figure 2, orange lines) gives similar age-specific patterns to those seen in Finland[26] and the Netherlands,[27] both of which have organized screening programs that stop at age 60 and low hysterectomy rates. The rebound in cervical cancers at older ages may be absent in Canadian and American registry rates due to a more gradual decline in screening participation reported with age and higher hysterectomy prevalences.[5,15]

A potential limitation of our analysis is that like most cervical cancer models we calibrated oncogenic progression risks 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 due to changes in sexual mores) while increased screening has reduced the cervical cancer risk over time.[7,28,29] It is challenging for decision models to account for these cohort effects because of a lack 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 rate in women 75-85 years old is slightly higher than that predicted by the model, likely 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 cancer incidence rates without screening to historical data from the 1950-60s and found a good match (Supplementary Appendix p.20). This suggests that despite cohort and period effects, our model reproduces well the natural history and risk of cervical cancer with and without screening. Our results therefore should be interpreted as the predicted future age-specific risk of cervical cancer risks assuming current rates of screening participation continue in the future. Our sensitivity analyses suggest that future increases in HPV prevalence due to cohort effects would also not substantially change our results. Another potential limitation of our model is that we assumed all women have the same average screening probability with the same test sensitivity. We therefore likely underestimate the number of women who never get 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, in order to provide cervical cancer risk estimates for these categories of women.

Very few studies of HPV infection and oncogenic progression have included elderly women. We therefore made the assumption that progression risks from infection to CIN in elderly women are similar to those measured in younger women. Empirical studies do not suggest that the type-specific rate of progression

from an infection varies substantially with age after conditioning on HPV type,[30-32] but none have studied elderly women specifically. Newly detected infections generally have a low risk of progressing to CIN in older women.[32] If oncogenic progression rates decline with age, then the remaining lifetime risk of cervical cancer would be even lower after a negative cytology or HPV test than our model predicts.

Due to the low sensitivity of a single cytology screen, some guidelines recommend a woman only stop screening after sufficient history of negative screens.[2,3] We did not assess this strategy as our model does not track the screening histories of women. Furthermore, as many women do not adhere to recommended screening intervals, many women will likely reach the age to end screening with an unknown or inadequate screening history. We found that for a typical woman with average screening adherence, a single negative cytology below age 70 would 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 indicated a very low remaining lifetime risk of cervical cancer. Though women past the age of 55 may have new HPV infections or reactivations later in life, our model predicts that these infections in most cases would not have time to progress to cervical cancer within her lifetime. These results are in agreement 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.[13,33]

The question of 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 as a benchmark the risk implicit in the existing accepted practice.[34] 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 (e.g. the current crude risk of cervical cancer after age 70 in Canada is approximately 0.3%).[35] 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,[34] so risks below this threshold could be considered consistent with the risk tolerance for a 3-5 year screening interval. It should be noted that the balance of harms and benefits of screening is another important consideration for any screening program;[2,3] the harms of screening older women include potential stress, pain, and discomfort caused by screening and false-positive results, as well as the costs of extending screening.

Aging populations are likely to see increased demand for the prevention of diseases in older age groups, so it is important to consider the added value of screening at older ages. Cervical cancer screening between the ages of 30-49 years old should always be the priority,[4] as screening between these ages likely prevents the most cervical cancers; our model simply predicts that there are also incremental benefits to continuing screening of women with cervices past these ages, though these benefits decline with age. Screening recommendations should not be made solely on the basis of cervical cancer incidence which include women with hysterectomies in the denominator, as these do not necessarily reflect cancer risks in older women women with a cervix who are the target of screening programs. Importantly, we found that an exit HPV test screening provides strong reassurance against cervical cancer past the age of 55, as women negative for HR HPV were predicted to be at very low risk of cervical cancer for the rest of their lives.

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 of the submitted work. MHM is a recipient of a Fonds de Recherche du Québec - Santé clinical research scholar salary award. CB has received speaker honorariums 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 of the submitted work. SK, WG, and LS have no conflicts of interest to disclose.

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AUTHORS' CONTRIBUTIONS

TM developed and calibrated the model. SK, ELF, MHM, 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 MHM, GO, LS, WG, and CB provided critical feedback on the analysis plan. TM ran the simulations, performed the analysis, and wrote the first draft of the manuscript. All authors reviewed the manuscript for intellectual content.

Table 1. Predicted remaining lifetime risk of cervical cancer for a woman with a cervix who stops screening at age 55 or 70, assuming she has typical screening adherence up to that age or has never been screened before, weighted average 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]
Typical screening rates up to given age[c]								
Stops screening	226	0·44%	443 [309-551]	1·0 [ref]	588	0·17%	170 [113-228]	1·0 [ref]
Cytology negative	440	0·23%	227 [161-281]	1/1·9 [$1{\cdot}8^{-1}$ to $2{\cdot}0^{-1}$]	1,206	0·08%	83 [56-111]	1/2·0 [$2{\cdot}0^{-1}$ to $2{\cdot}1^{-1}$]
HPV test negative	1,940	0·05%	52 [27-87]	1/8·9 [$5{\cdot}3^{-1}$ to $15{\cdot}7^{-1}$]	6,525	0·02%	15 [4-35]	1/12·9 [$5{\cdot}3^{-1}$ to $40{\cdot}5^{-1}$]
Co-test negative	2,253	0·04%	44 [26-67]	1/10·2 [$6{\cdot}7^{-1}$ to $16{\cdot}6^{-1}$]	9,550	0·01%	10 [4-22]	1/18·1 [$8{\cdot}3^{-1}$ to $44{\cdot}0^{-1}$]
True normal[d]	2,402	0·04%	42 [27-62]	1/10·8 [$6{\cdot}4^{-1}$ to $16{\cdot}5^{-1}$]	13,678	0·01%	7 [4-12]	1/24·8 [$11{\cdot}7^{-1}$ to $43{\cdot}7^{-1}$]
Never screened before[e]								
Remains unscreened	66	1·52%	1,525 [899-2,344]	1·0 [ref]	125	0·80%	803 [383-1,351]	1·0 [ref]
Cytology negative	120	0·83%	830 [545-1,233]	1/1·8 [$1{\cdot}6^{-1}$ to $2{\cdot}0^{-1}$]	246	0·41%	407 [212-682]	1/2·0 [$1{\cdot}8^{-1}$ to $2{\cdot}0^{-1}$]
HPV test negative	1,096	0·09%	91 [29-213]	1/18·2 [$9{\cdot}2^{-1}$ to $42{\cdot}8^{-1}$]	2,167	0·05%	46 [6-128]	1/21·3 [$8{\cdot}3^{-1}$ to $108{\cdot}9^{-1}$]
Co-test negative	1,504	0·07%	66 [27-133]	1/24·1 [$14{\cdot}4^{-1}$ to $49{\cdot}2^{-1}$]	3,838	0·03%	26 [5-68]	1/36·3 [$15{\cdot}7^{-1}$ to $150{\cdot}1^{-1}$]

HPV=human papillomavirus; ref=reference scenario·

[a] Numbers in brackets are the minimum and maximum 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] Risk for a woman with a cervix with average lifetime screening rates up to age 55 or 70, and who stops screening without considering previous test results (stops screening) or who receives a negative exit screen test result·

[d] Hypothetical scenario of remaining lifetime risks for a true cytological normal woman with a cervix at age 55 or 70 who stops screening· Reflects maximum potential risk reduction if a long history of negative cytology tests is assumed to identify true normal women·

[e] Risk for a woman with a cervix who has never screened before, and who will remain never screened (remains unscreened) or who receives a negative screen result for the first time at a given age·

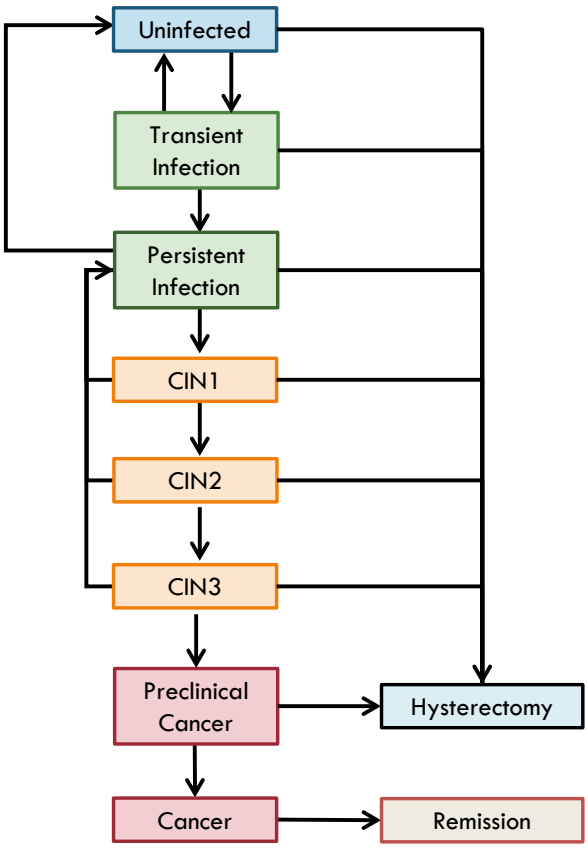

Figure 1. Model natural history structure. Boxes represent mutually exclusive health states, arrows represent possible transitions between health states. There is also a Death state (not pictured) to which all health states may transition. Cohorts enter the model in the Uninfected health state. CIN=cervical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

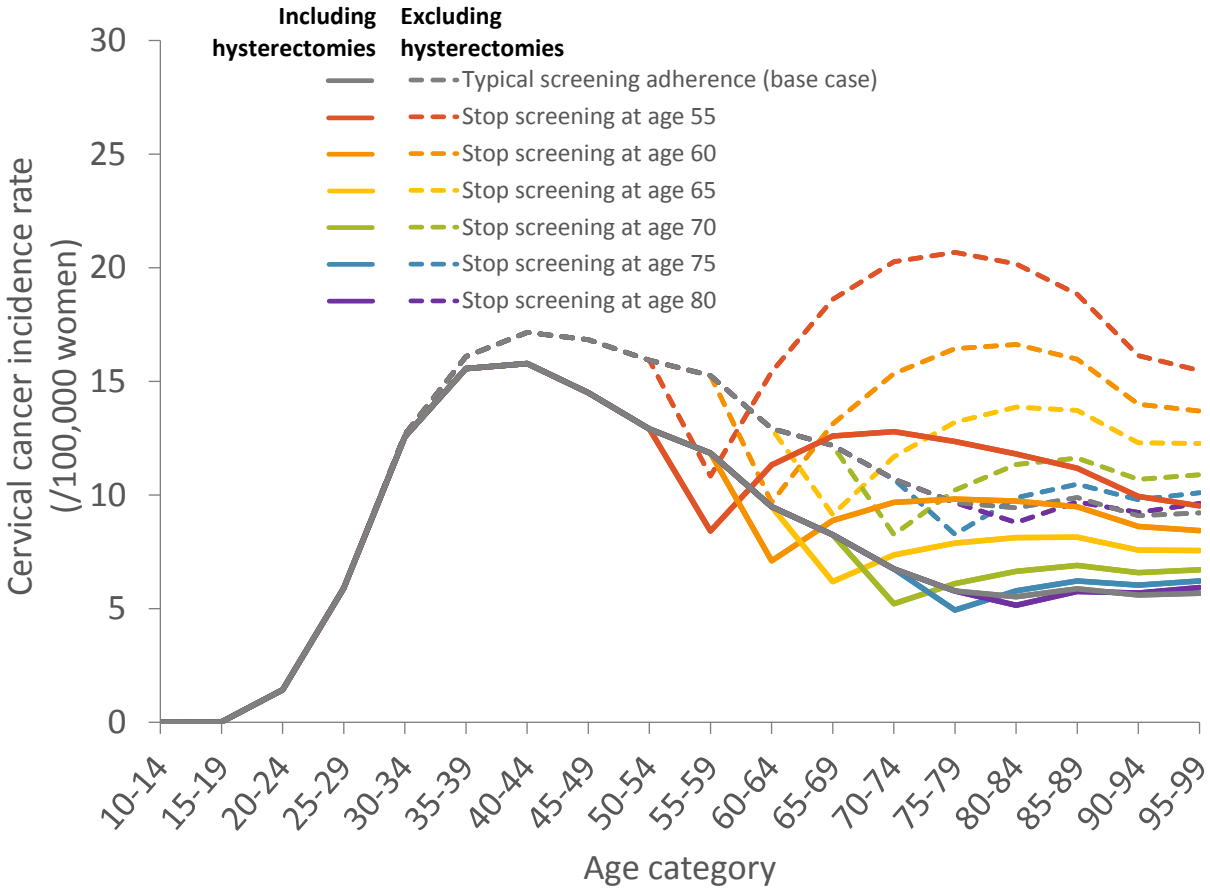

Figure 2. Model-predicted age-specific cervical cancer incidence rates, with the denominator including (solid lines) and excluding (dashed lines) women with hysterectomies. Typical screening adherence refers to the base case scenario using average age-specific cytology screening rates. Other scenarios show model predictions if women have average age-specific cytology screening rates 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.

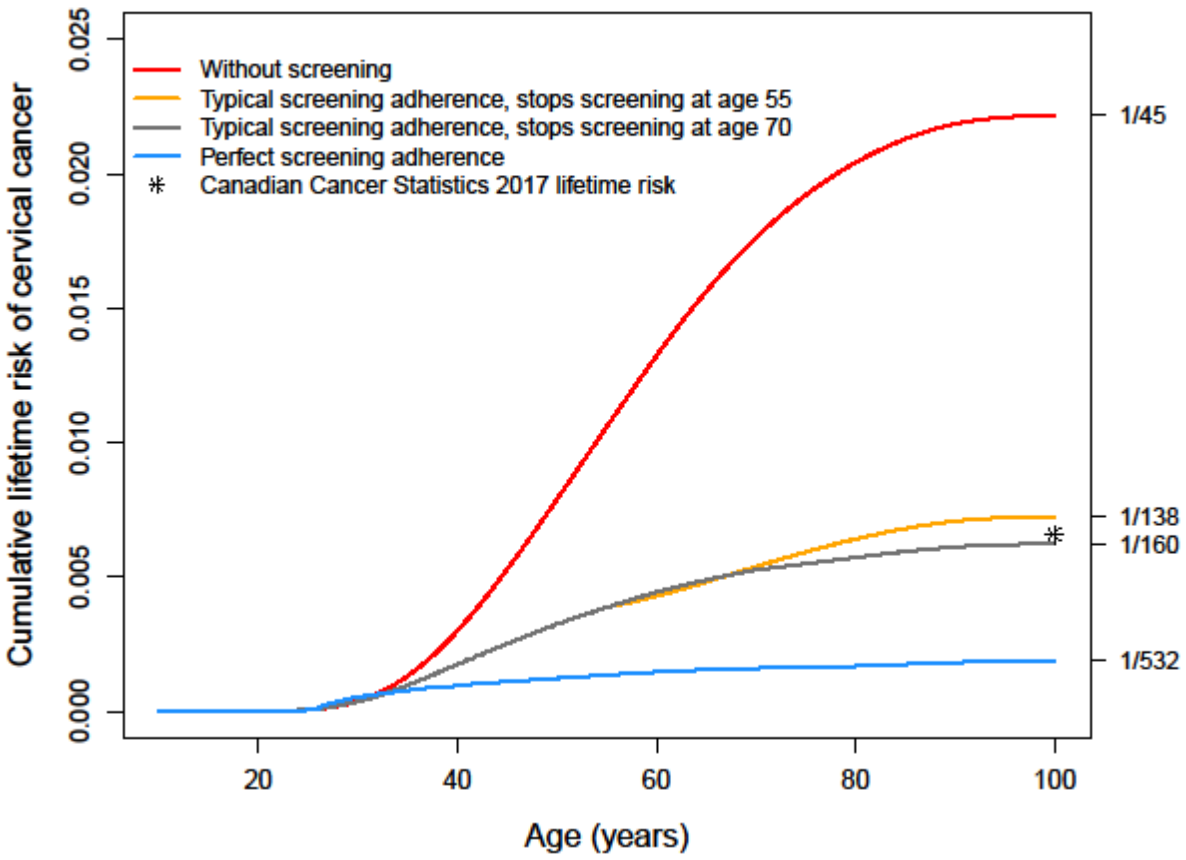

Figure 3. Model-predicted cumulative cervical cancer lifetime risk by age (solid lines), compared to current lifetime risk of 1/152 women estimated in Canadian Cancer Statistics 2017 (star).[35] Estimates are meant to represent the crude lifetime risk at birth and therefore do not exclude hysterectomies (the denominator is the total size of the cohort at 10 years old). Scenarios where screening stops at age 55 and 70 assume average age-specfic screening adherence rates up to these ages, and no screening thereafter.

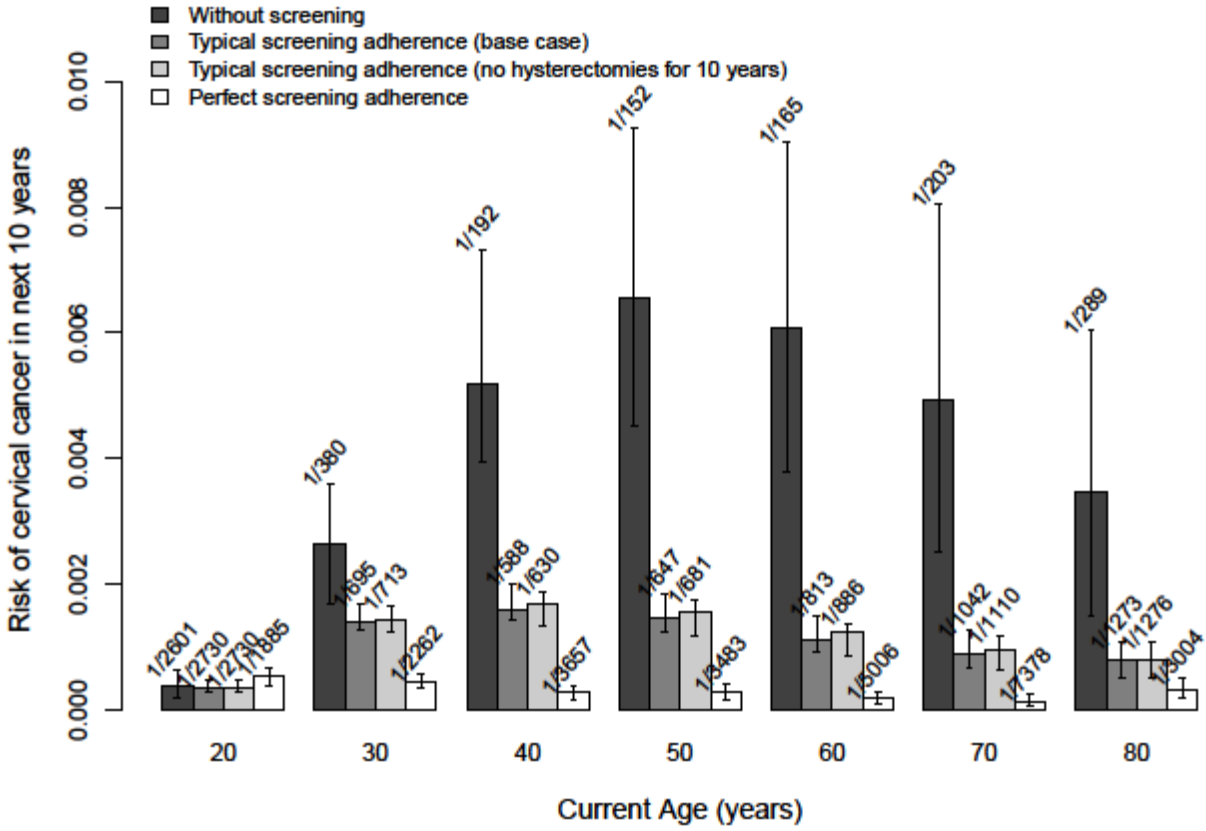

Figure 4. Risk of developing cervical cancer during the next 10 years for a woman at a given age with a cervix. Denominators are the number of women who have a cervix at the start of each 10 years. "Without screening": risk for a woman with a cervix who will never screen. "Typical screening adherence (base case)": risk for a woman with average screening rates who currently has a cervix. "Typical screening adherence (no hysterectomies for 10 years)": risk for a woman with average screening adherence who currently has a cervix, and additionally assuming she will not undergo a hysterectomy during the next 10 years. "Perfect screening adherence": risk for a woman who currently has a cervix and who screens with cytology every 3 years from 25-69 years, at which point she stops screening. Columns and fractions are the weighted average of 55 parameter sets, and error bars are the minimum and maximum predictions of 55 parameter sets. The slight increase in the 10-year risk at age 20 with perfect screening adherence is due to a combination of 1) lack of prevention in <25 year olds and 2) lead time due to detection of more preclinical cancers in 25-29 year olds than in other scenarios.

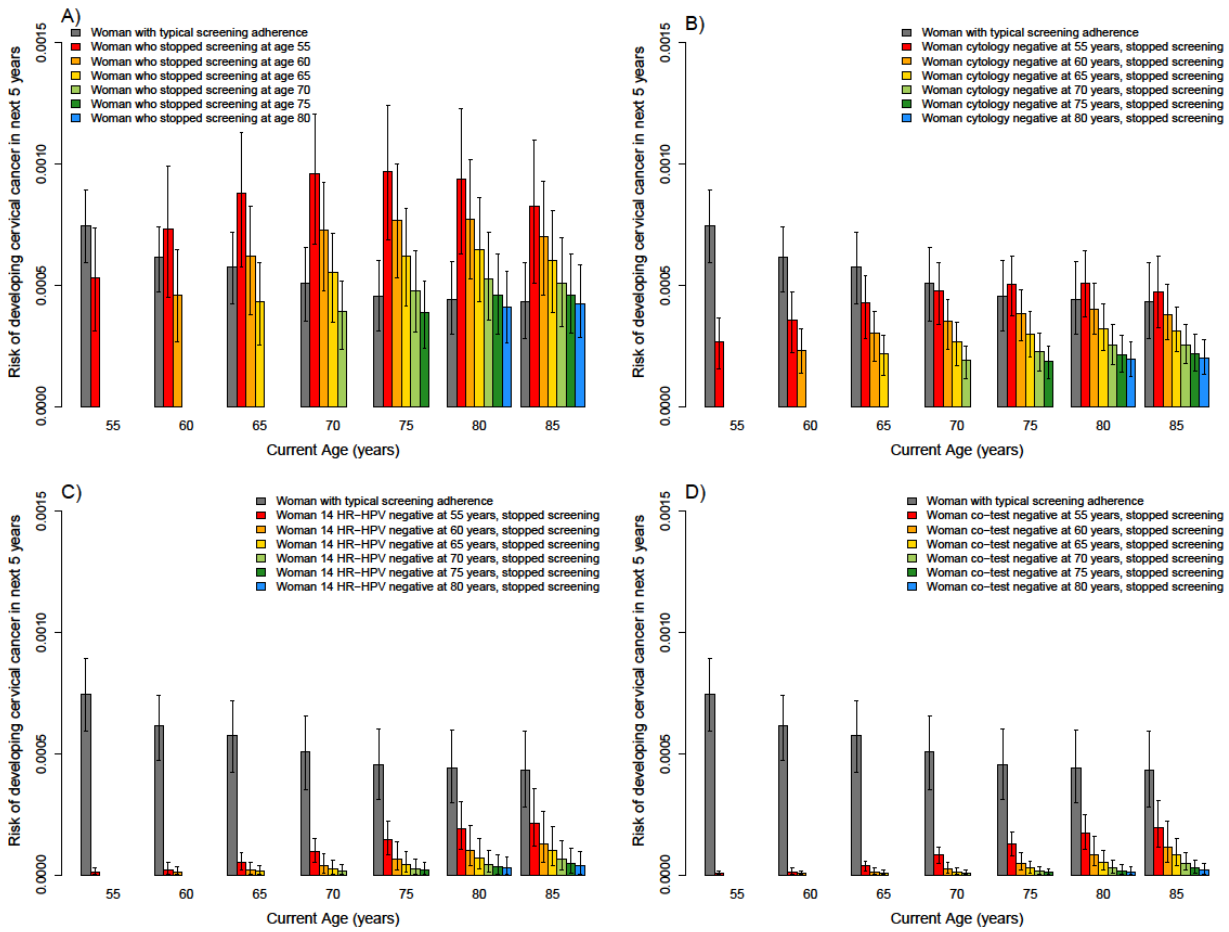

Figure 5. Risk of developing cervical cancer in the next 5 years for a woman with typical screening adherence and who still has her cervix, if she stops screening at a given age A) regardless of screening history, B) after a negative cytology result, C) after a HPV test negative for 14 HR HPV types, and D) after a negative cotest (cytology and HPV test for 14 HR HPV types). The x-axis represents the woman's current age, bars represent the age at which she stopped screening. Grey represents the risk for a typical woman who has average screening rates. Columns are the weighted average and error bars are the minimum and maximum predictions of 55 parameter sets. We assumed the HPV test has 100% sensitivity to detect 14 oncogenic HPV types (HPV-16/18/31/33/35/39/45/51/52/56/58/59/66/68).

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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 appendix, originally published in The Lancet Oncology on November 01st 2018:
https://doi.org/10.1016/S1470-2045(18)30536-9

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 [$1{\cdot}8^{-1}$ to $2{\cdot}0^{-1}$]	1098	0·09%	91 [63-117]	1/2·0 [$2{\cdot}0^{-1}$ to $2{\cdot}1^{-1}$]
HPV test negative	1478	0·07%	68 [39-103]	1/8·3 [$5{\cdot}3^{-1}$ to $13{\cdot}8^{-1}$]	5868	0·02%	17 [6-35]	1/12·8 [$5{\cdot}6^{-1}$ to $28{\cdot}2^{-1}$]
Co-test negative	1703	0·06%	59 [37-83]	1/9·5 [$6{\cdot}3^{-1}$ to $14{\cdot}5^{-1}$]	8562	0·01%	12 [5-23]	1/17·8 [$8{\cdot}9^{-1}$ to $36{\cdot}7^{-1}$]
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 [$1{\cdot}8^{-1}$ to $2{\cdot}0^{-1}$]	1138	0·09%	88 [61-113]	1/2·0 [$2{\cdot}0^{-1}$ to $2{\cdot}1^{-1}$]
HPV test negative	1650	0·06%	61 [35-92]	1/8·5 [$5{\cdot}4^{-1}$ to $14{\cdot}2^{-1}$]	6108	0·02%	16 [6-34]	1/12·8 [$5{\cdot}6^{-1}$ to $28{\cdot}4^{-1}$]
Co-test negative	1907	0·05%	52 [33-74]	1/9·7 [$6{\cdot}5^{-1}$ to $14{\cdot}9^{-1}$]	8923	0·01%	11 [5-22]	1/17·9 [$8{\cdot}9^{-1}$ to $36{\cdot}9^{-1}$]
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 [$1{\cdot}7^{-1}$ to $1{\cdot}9^{-1}$]	1118	0·09%	89 [62-112]	1/2·3 [$2{\cdot}3^{-1}$ to $2{\cdot}4^{-1}$]
HPV test negative	1162	0·09%	86 [53-124]	1/5·7 [$3{\cdot}9^{-1}$ to $8{\cdot}7^{-1}$]	4569	0·02%	22 [10-39]	1/10·2 [$5{\cdot}8^{-1}$ to $19{\cdot}7^{-1}$]
Co-test negative	1266	0·08%	79 [51-109]	1/6·2 [$4{\cdot}2^{-1}$ to $9{\cdot}0^{-1}$]	5864	0·02%	17 [9-28]	1/12·8 [$8{\cdot}1^{-1}$ to $22{\cdot}1^{-1}$]
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 [$1{\cdot}5^{-1}$ to $1{\cdot}5^{-1}$]	600	0·17%	167 [122-213]	1/1·6 [$1{\cdot}5^{-1}$ to $1{\cdot}6^{-1}$]
HPV test negative	1729	0·06%	58 [32-94]	1/11·1 [$6{\cdot}7^{-1}$ to $19{\cdot}3^{-1}$]	5042	0·02%	20 [6-42]	1/15·5 [$6{\cdot}5^{-1}$ to $41{\cdot}1^{-1}$]
Co-test negative	1971	0·05%	51 [29-78]	1/12·5 [$8{\cdot}1^{-1}$ to $20{\cdot}4^{-1}$]	6711	0·01%	15 [5-31]	1/20·0 [$9{\cdot}1^{-1}$ to $46{\cdot}8^{-1}$]
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 [$2{\cdot}2^{-1}$ to $2{\cdot}8^{-1}$]	2494	0·04%	40 [27-52]	1/2·8 [$2{\cdot}6^{-1}$ to $3{\cdot}0^{-1}$]
HPV test negative	2118	0·05%	47 [28-69]	1/7·1 [$4{\cdot}5^{-1}$ to $11{\cdot}4^{-1}$]	8087	0·01%	12 [5-25]	1/10·5 [$4{\cdot}9^{-1}$ to $22{\cdot}3^{-1}$]
Co-test negative	2456	0·04%	41 [26-56]	1/8·2 [$5{\cdot}1^{-1}$ to $12{\cdot}2^{-1}$]	12507	0·01%	8 [4-15]	1/15·5 [$8{\cdot}3^{-1}$ to $29{\cdot}2^{-1}$]

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

CONTENTS

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

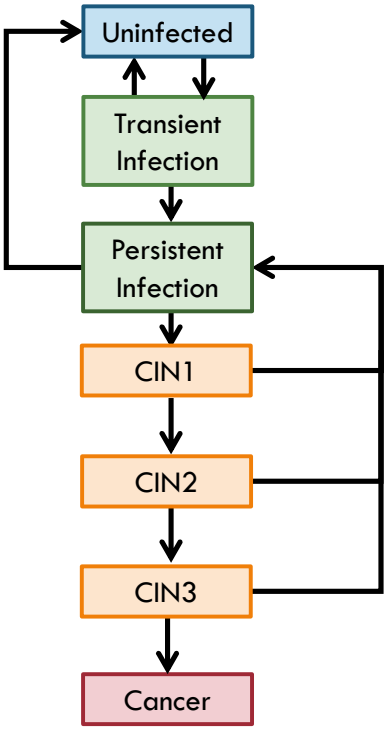

Figure 1. Natural history of cervical cancer without any intervention.

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.

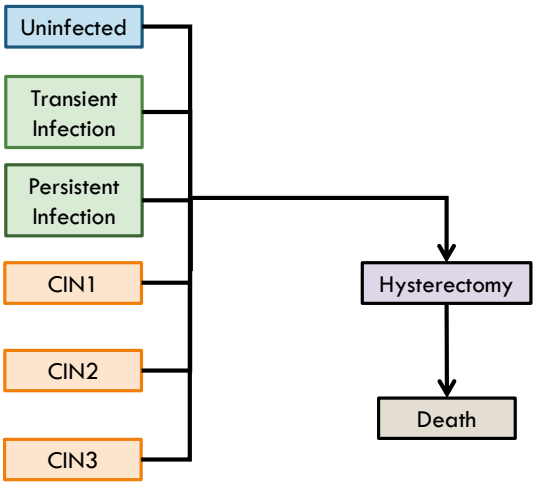

Figure 2. Background hysterectomies.

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.

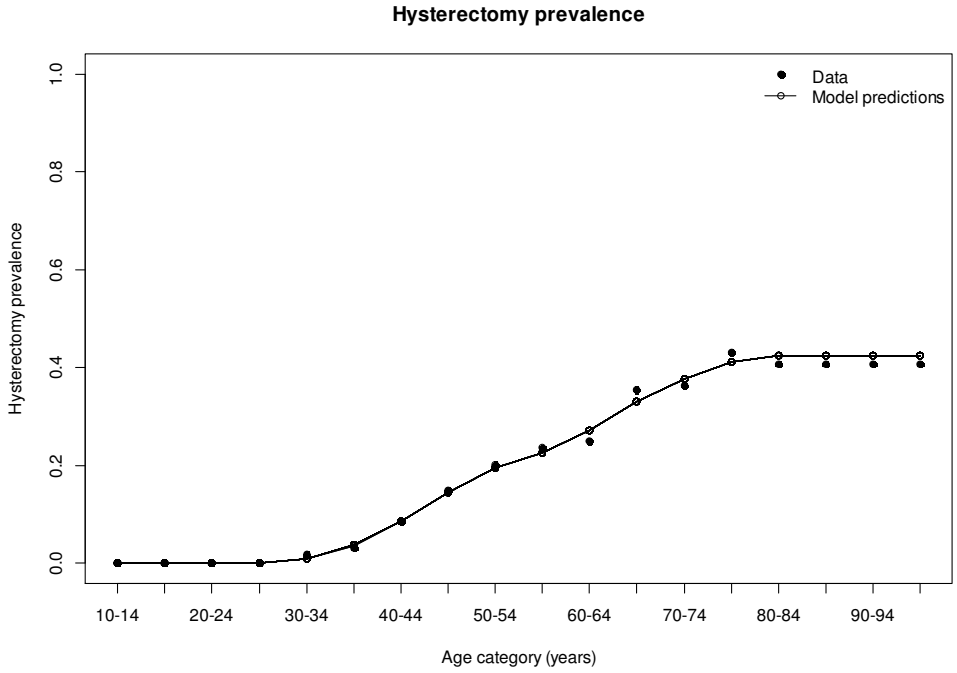

Figure 3. Age-specific cumulative proportion of women having had a total hysterectomy.
The line (Model) represents the modelled prevalence of hysterectomy compared to the points (Data) which are the self-reported hysterectomies in the Canadian Community Health Survey 2014 annual component.[2] We assumed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

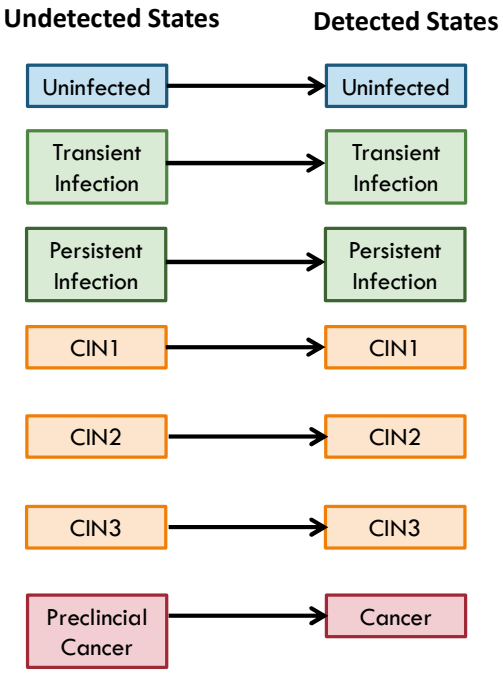

Figure 4. Screening and symptoms transform Undetected states into Detected states.

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.

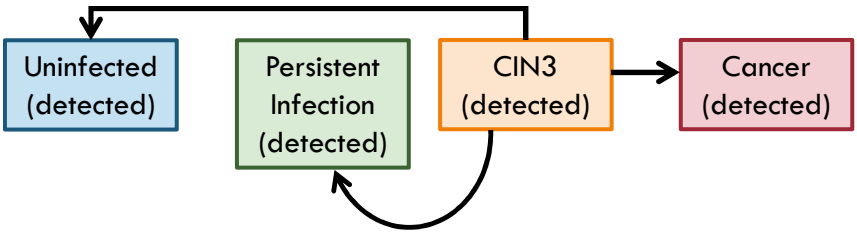

Figure 5. CIN treatment outcomes, using CIN3 as an example.
CIN3 that does not get removed by treatment has the same probability of progressing to Cancer or regressing to Persistent Infection in absence of treatment.

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.

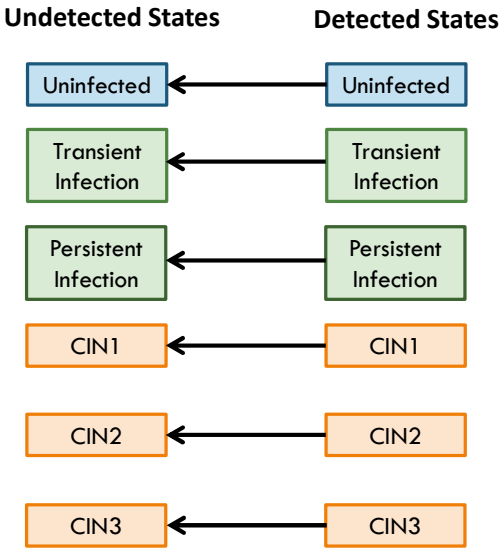

Figure 6. Loss to follow-up and returns to the regular screening population.

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).

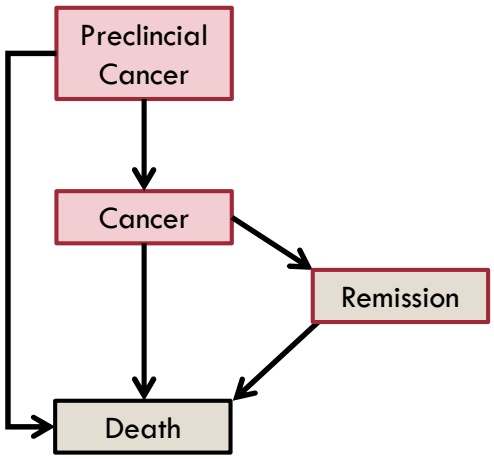

Figure 7. Cancer treatment and survival.

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

	Priors			
Parameter	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.

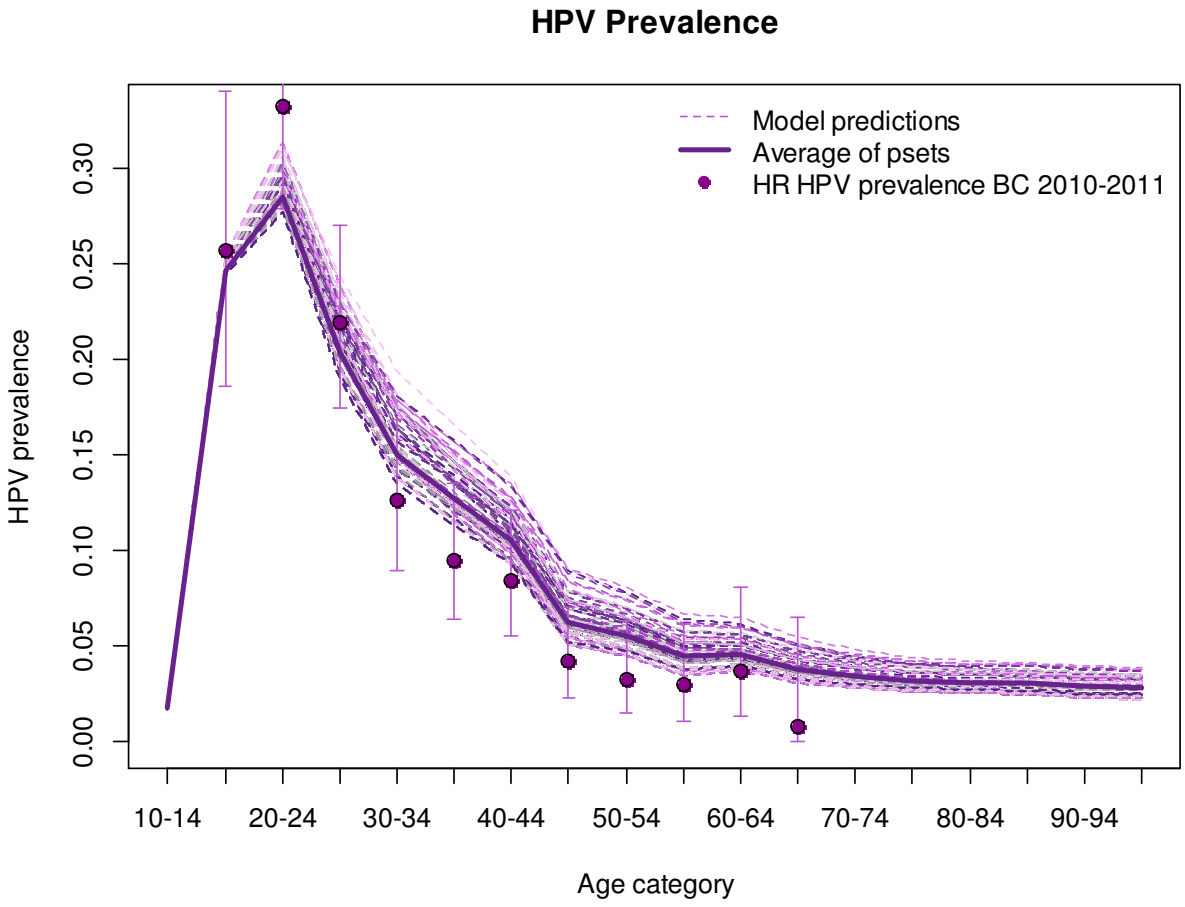

Figure 8. HR HPV prevalence.
Model predictions are compared to HR Hybrid Capture 2 positivity in a population-based sample of the British Columbia screening population (Ogilvie *et al.*).[12]

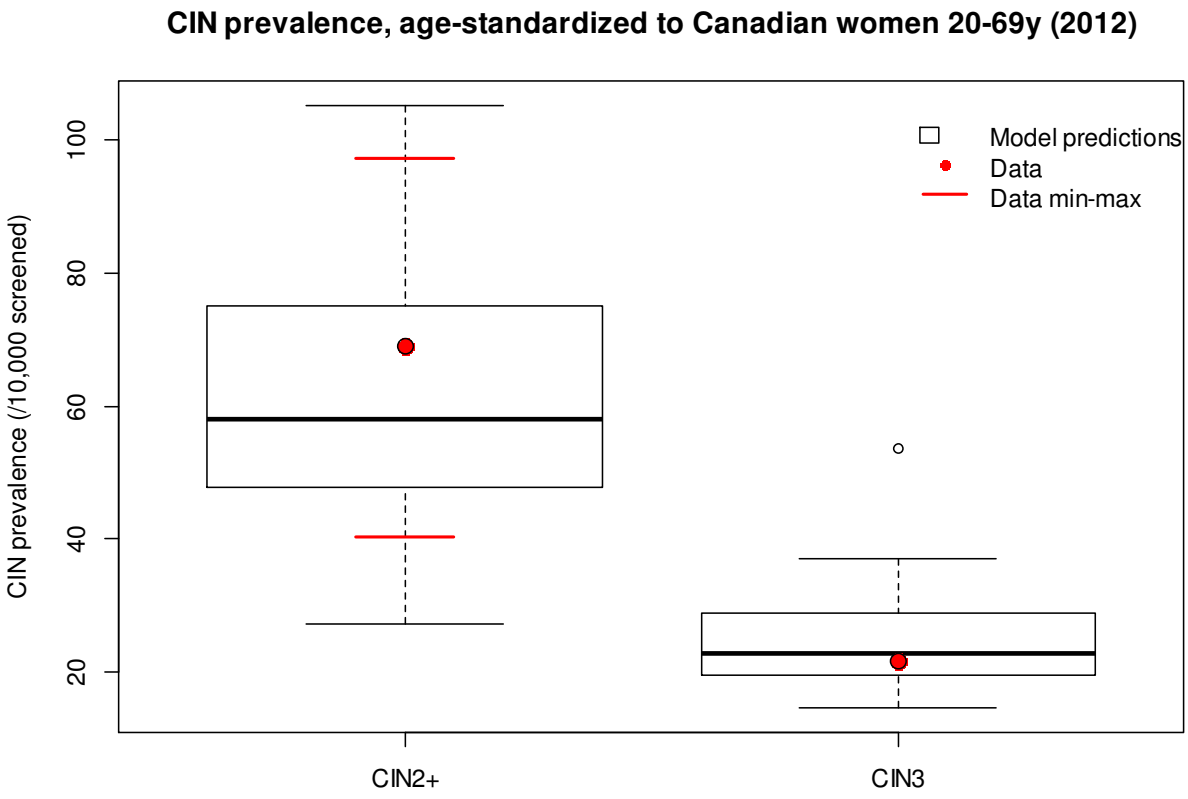

Figure 9. CIN2+ and CIN3 prevalence per 10,000 women screened.
Model prediction were age-standardized to the Canadian female population 20-69 years old and compared to the CIN2+ prevalence in British Columbia[5] and the CIN3/AIS prevalence in Ontario.[23] Min-max values were obtained by age-standardizing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

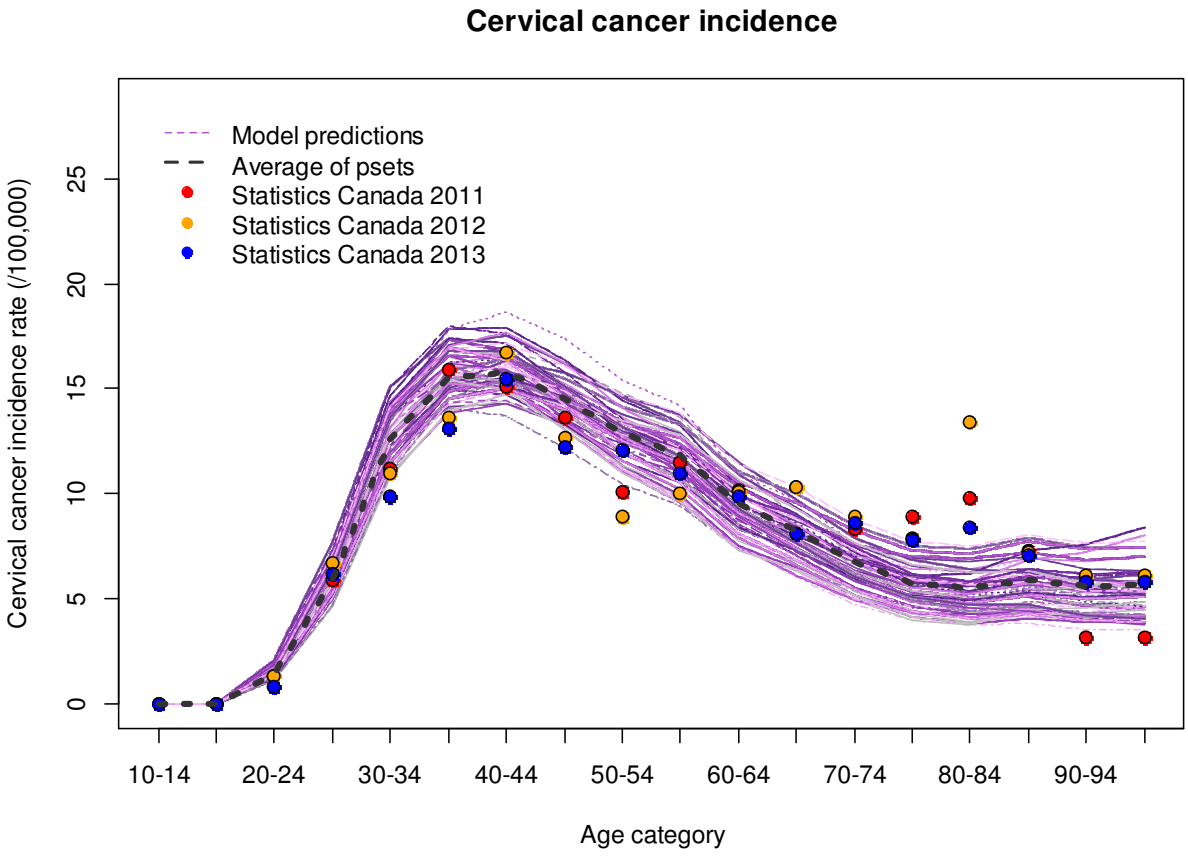

Figure 10. Cervical cancer incidence rates.
Each line represents one of 55 unique parameter sets. Model predictions are compared to 2011-2013 data from CANSIM Table 103-0550.[27]

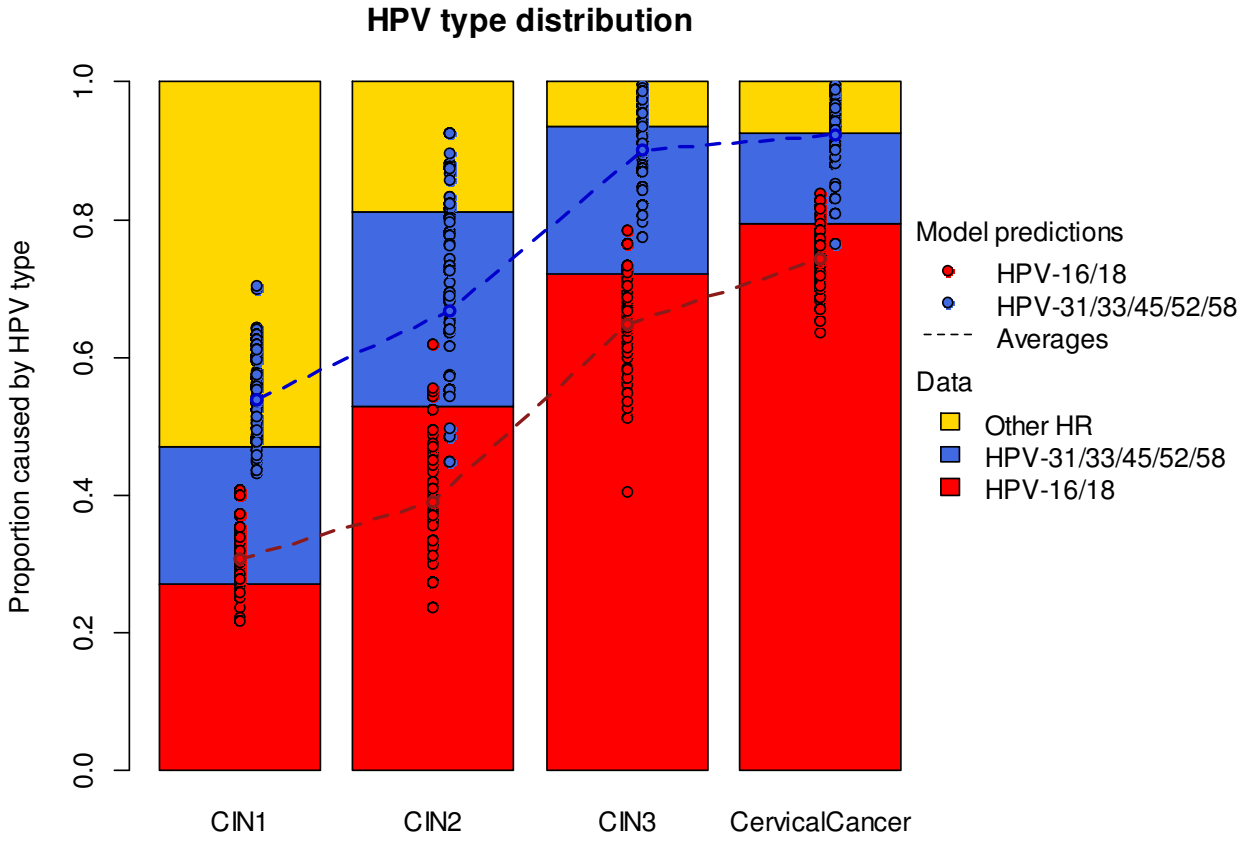

Figure 11. HPV type distribution in CIN and cervical cancer.
Each dot represents one of 55 unique parameter sets. Model predictions are compared to the type distribution in a sample of Canadian CIN and cervical cancer cases (Coutlée *et al.* 2011).[18] HPV type distributions have been redistributed over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

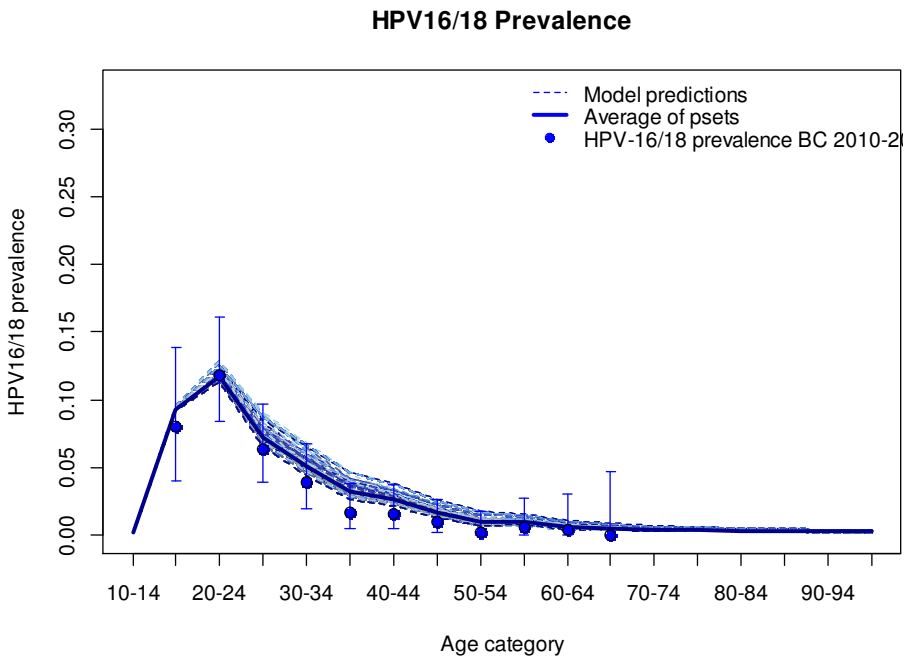

Figure 12. HPV16/18 prevalence by age.
Model predictions are compared to Roche Linear Array positivity in a population-based sample of the British Columbia screening population (Ogilvie *et al.*).[12]

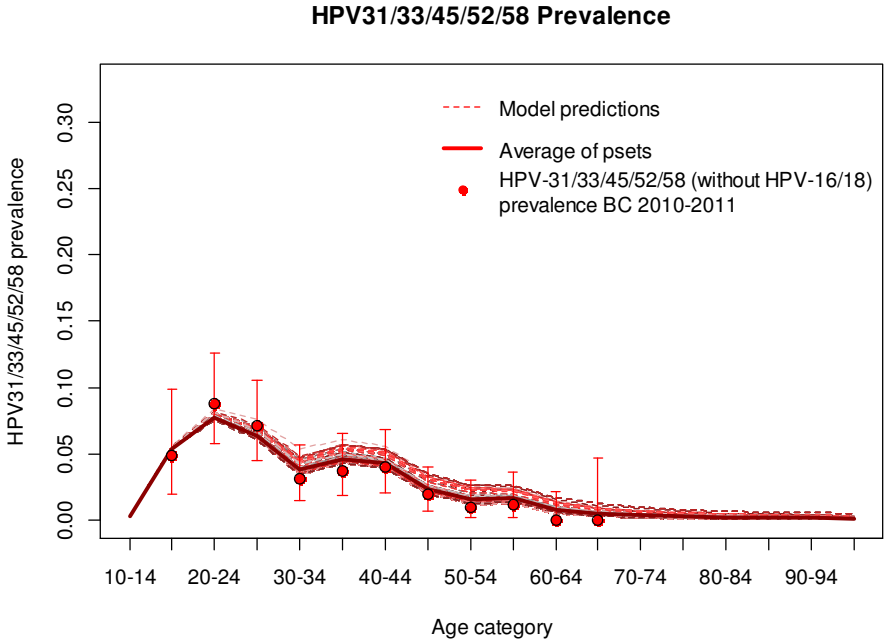

Figure 13. HPV31/33/45/52/58 prevalence by age.
Model predictions are compared to Roche Linear Array positivity for infection with HPV31/33/35/52/58 (excluding co-infections with HPV16/18) in a population-based sample of the British Columbia screening population (Ogilvie *et al.*).[12]

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).

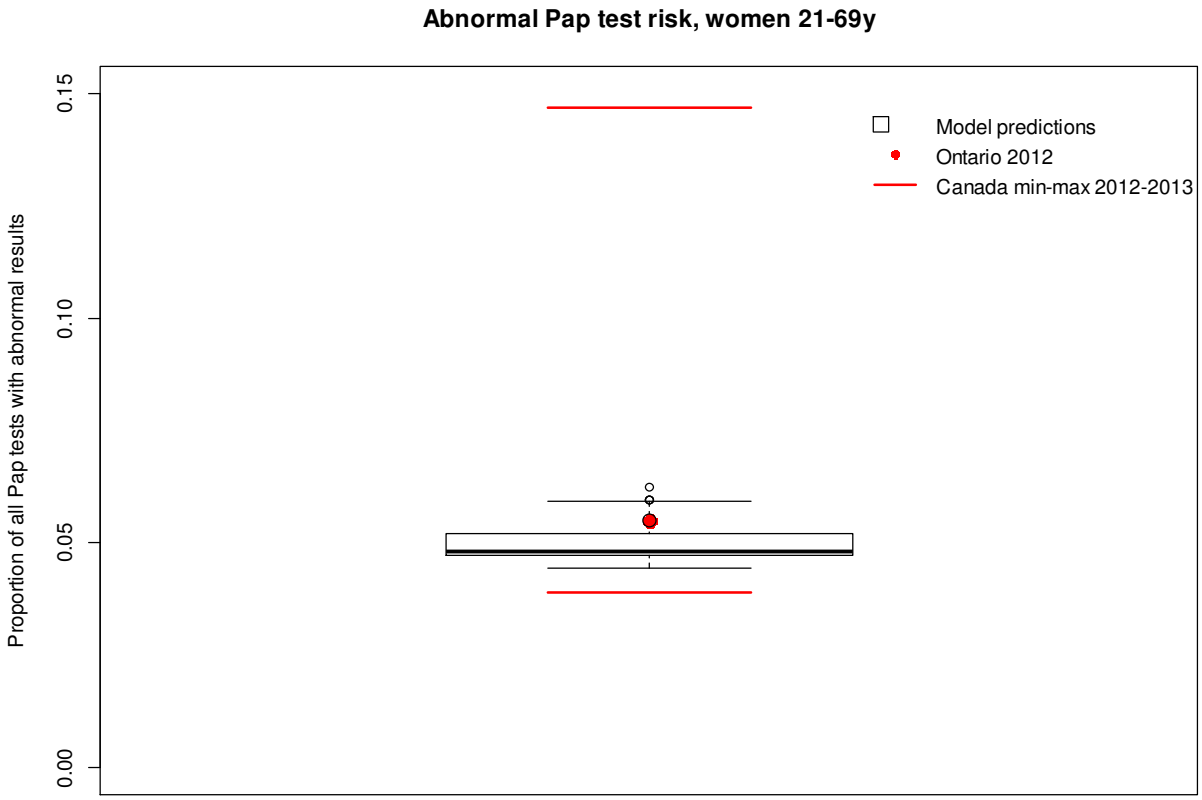

Figure 14. Proportion of screening tests that have abnormal results.
Model predictions are age-standardized and compared to the Ontario proportion of screen-eligible women who have had an abnormal Pap test result (>=ASCUS) in 2012.[23] The min-max interval corresponds to the minimum and maximum across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

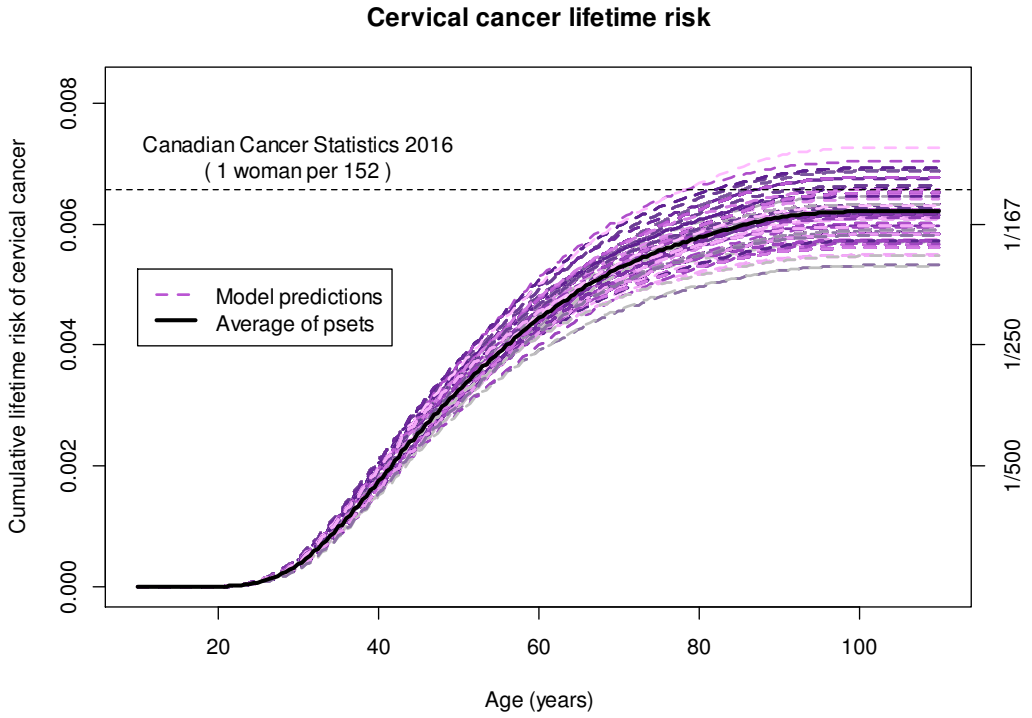

Figure 15. Cumulative cervical cancer risk by age.
Model predictions are compared to the estimated lifetime probability of developing cervical cancer in Canada in 2010.[6]

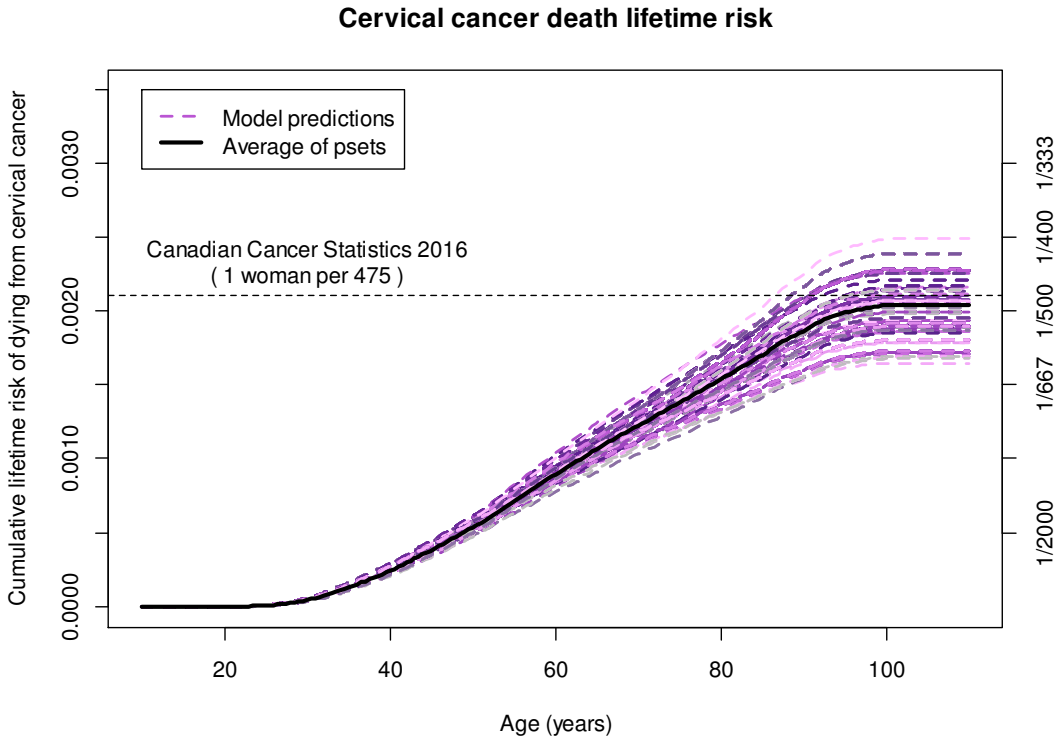

Figure 16. Cumulative cervical cancer death risk by age.
Model predictions are compared to the estimated lifetime probability of dying of cervical cancer in Canada in 2010.[6]

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).

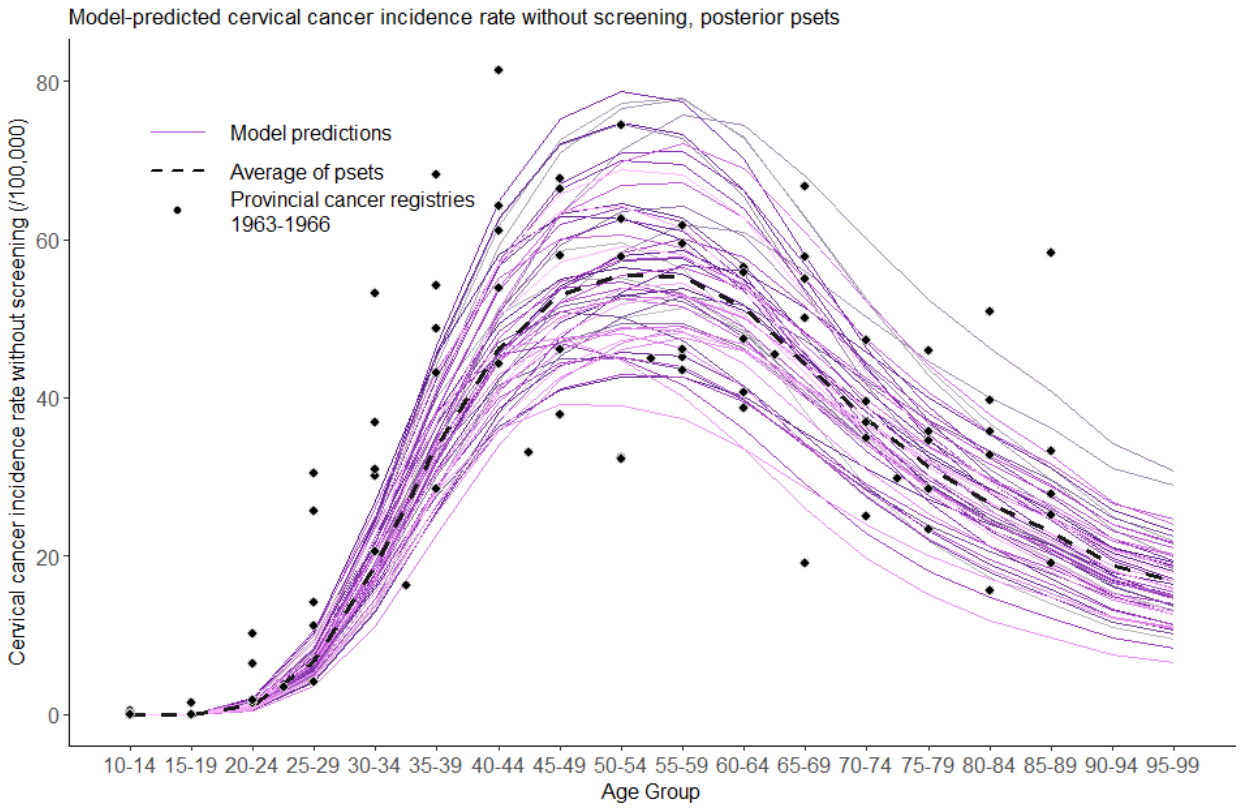

Figure 17. Cervical cancer incidence rate predicted without screening.
Model predictions are compared to cervical cancer incidence rates from provincial cancer registries from 1963-1966[31] and the 1955-1957 incidence rates from BC.[30] Black points correspond to data from individual registries.

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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