# Age at last screening and remaining lifetime risk of cervical cancer in older, unvaccinated, HPV-negative 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.

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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

## 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.

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 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).

See Online for appendix

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 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 intraepithelia 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

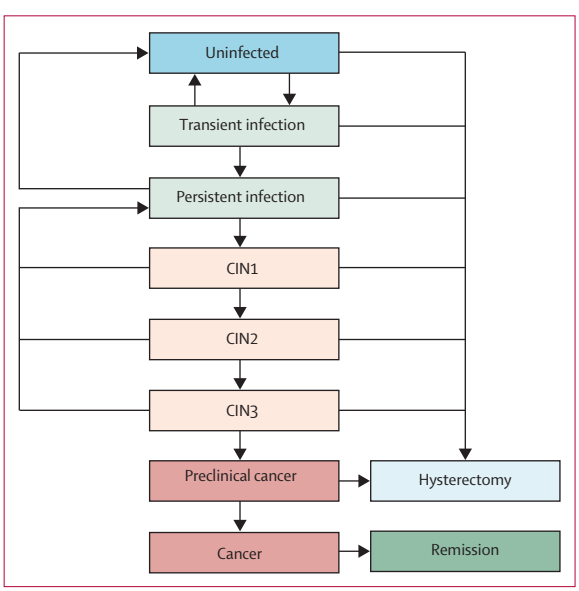


***Figure 1:*** **Model natural history structure**
Boxes represent mutually exclusive health states and arrows represent possible transitions between health states. There is also a death state (not pictured) to which all health states could transition. Cohorts enter the model in the uninfected health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

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 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).

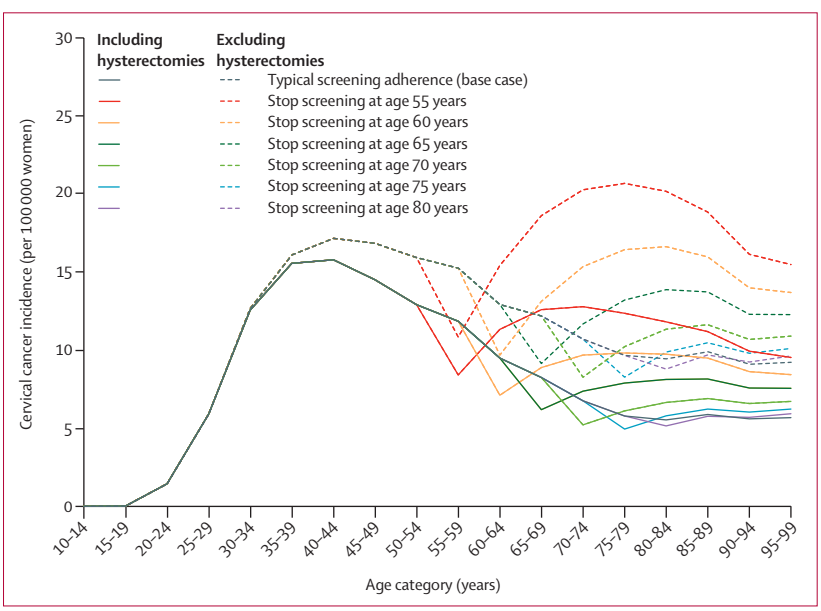


*Figure 2:* **Model-predicted age-specific cervical cancer incidence**
Lines show incidence when the denominator included (solid lines) and excluded (dashed lines) women with hysterectomies. Typical screening adherence refers to the base case scenario using average age-specific cytology screening. Other 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.

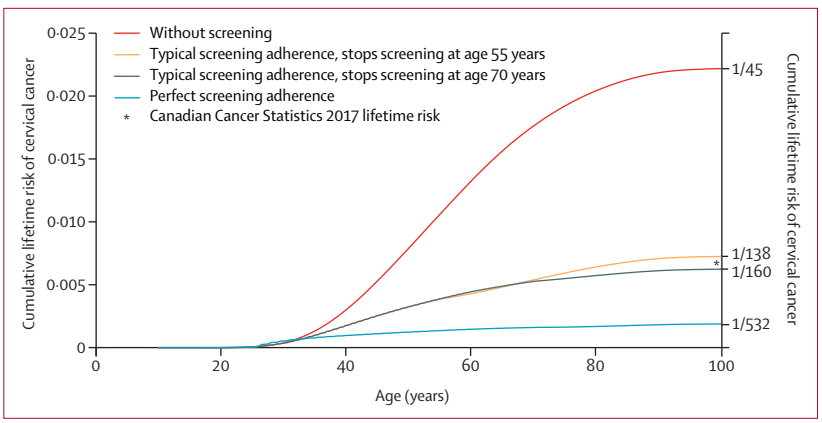


***Figure 3:*** **Model-predicted cumulative cervical cancer lifetime risk**
Data show risk for no screening, typical screening adherence with screening stopped at specific ages, and perfect adherence. Estimates represent the crude lifetime risk at birth and therefore do not exclude hysterectomies (the 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.

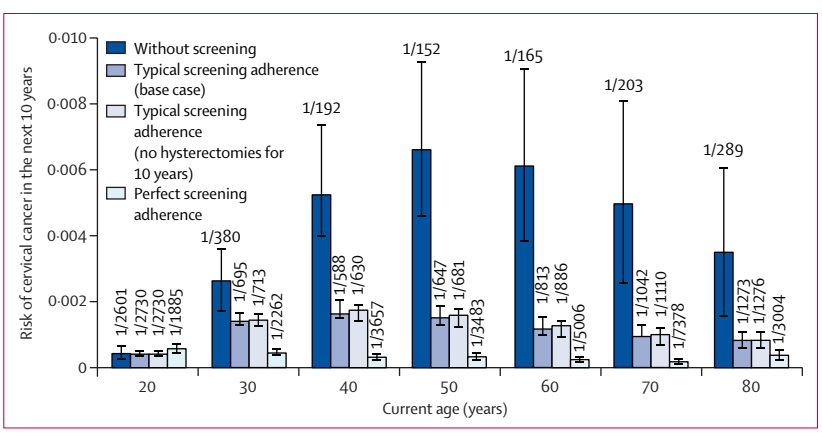


***Figure 4:*** **Prospective risk of cervical cancer during the next 10 years for women with a cervix at a given age**
Data are the weighted mean and error bars represent 95% percentile interval of predictions of 55 unique parameter sets. Denominators are the number of women with a cervix at the start 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.

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

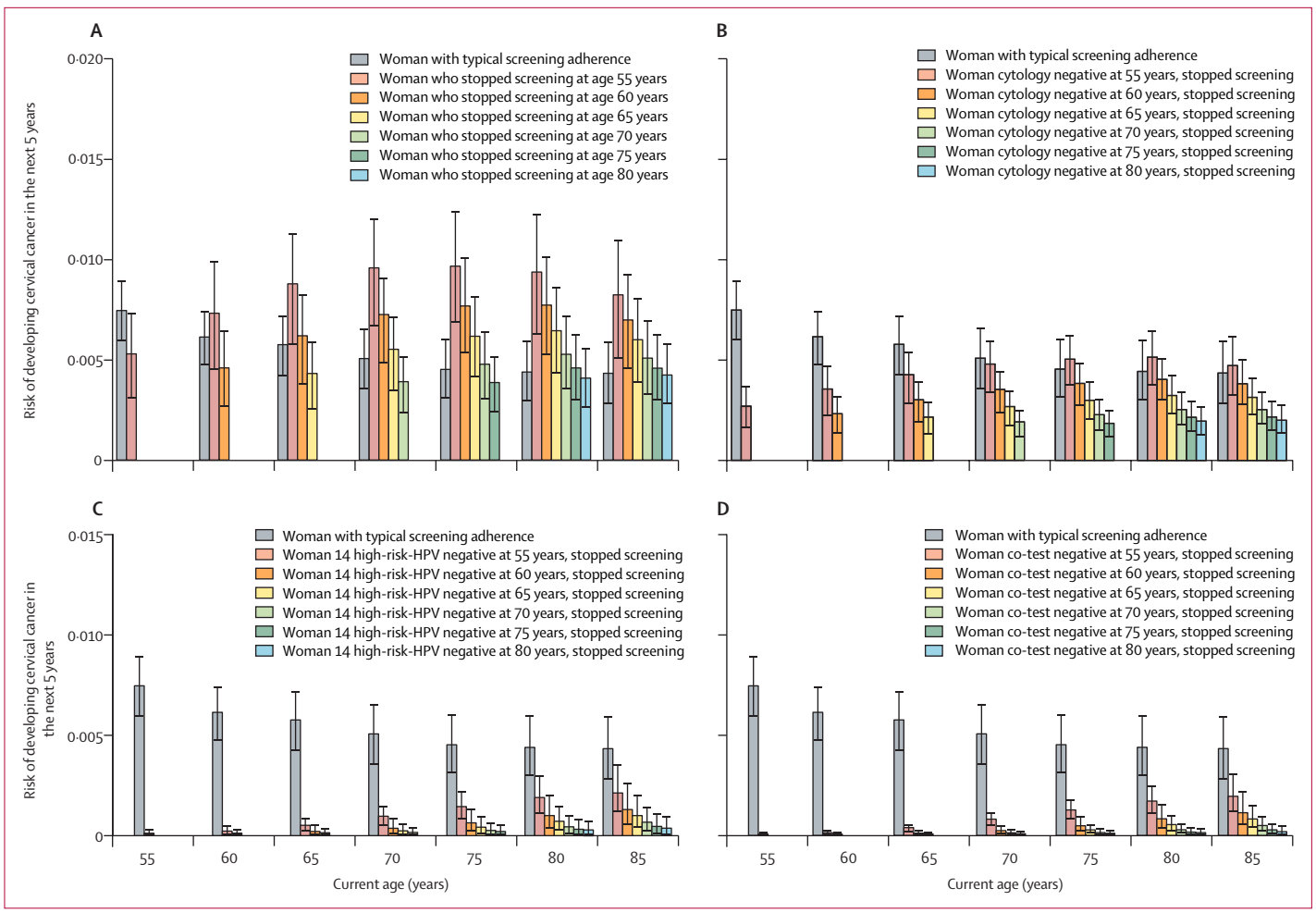


***Figure 5:*** **Risk of developing cervical cancer in the next 5 years for women with typical screening adherence and who have a cervix, if screening is stopped at a given age**
Data are the weighted mean and error bars represent the 95% percentile interval of predictions of 55 unique parameter sets. 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.

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 (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,

| | 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**

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; 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.

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