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Modeling the Balance of Benefits and Harms of Cervical Cancer Screening with Cytology and Human Papillomavirus Testing

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ABSTRACT

Background: Benefits of screening should outweigh its potential harms. We compared various metrics to assess the balance of benefits and harms of cervical cancer screening.

Methods: We used a cervical cancer natural history Markov model calibrated to the Canadian context to simulate 100,000 unvaccinated women over a lifetime of screening with either cytology every 3 years or human papillomavirus (HPV) testing every 5 years. We estimated the balance of benefits and harms attributable to screening using various metrics, including colposcopies/life-year gained, and net lifetime quality-adjusted life-years (QALY) gained, a measure integrating women's health preferences. We present the average (minimum–maximum) model predictions.

Results: Cytology-based screening led to 1,319,854 screening tests, 30,395 colposcopies, 13,504 life-years gained over a lifetime, 98 screening tests/life-year gained, 2.3 (1.6–3.3) colposcopies/life-year gained, and a net lifetime gain of 10,735 QALY (5,040–17,797). HPV-based screening with cytology triage in the same population would lead to 698,250 screening tests, 73,296 colposcopies, 15,066 life-years gained over a lifetime, 46 screening tests/life-year gained, 4.9 colposcopies/life-year gained (2.9–11.1), and a net lifetime gain of 11,690 QALY (4,409–18,742). HPV-based screening was predicted to prevent more cancers, but also incur more screening harms than cytology-based screening.

Conclusions: Metrics using colposcopies as the main harm outcome favored cytology-based screening, whereas metrics based on screening tests and health preferences tended to favor HPV-based screening strategies.

Impact: Whether HPV-based screening will improve the balance between benefits and harms of cervical cancer screening depends on how the balance between benefits and harms is assessed.

Introduction

Screening procedures may incur harm for some individuals, such as discomfort, psychological stress, and adverse physical side effects (1, 2). However, screening may be justified if the expected preventive benefits from early detection are considered greater than the expected health harms (3). Screening with cytology testing has substantially reduced cervical cancer incidence and mortality in many countries and is widely considered by policy-makers to incur more benefits than harms (4, 5). Cervical cancer screening recommendations have nonetheless been modified over the years to improve its balance of benefits and harms. For example, yearly screening is increasingly discouraged by many guidelines in favor of longer screening intervals due to lack of benefit and to reduce the harms of over-screening (4, 6). The replacement of cytology with human papillomavirus (HPV) testing as the primary screening test in many countries now promises to fundamentally change the balance of benefits and harms of cervical cancer screening. Clinical trials have shown that HPV testing has a higher sensitivity but lower specificity than cytology, leading to a higher colposcopy referral rate, but less high-grade lesion diagnoses in subsequent rounds (7–10). However, there remains uncertainty on whether HPV-based screening will improve the balance of benefits and harms of screening for women over a lifetime.

Decision models are increasingly used to aid decision-making because they can link intermediate endpoints from trials with long-term clinical outcomes, and compare multiple potential screening strategies using a common analytical framework (11). Notably, the US Preventive Services Task Force (USPSTF) and Cancer Council Australia have used both empirical and decision model evidence to examine the impacts of potential screening strategies when updating their latest cervical cancer screening recommendations (12–14). The USPSTF specifically from 2012 onward opted to use in decision models a quantitative metric to contrast benefits and harms of screening, the number of colposcopies per life-year gained (12, 15). We refer in this paper to such metrics, which contrast benefit outcomes with harm outcomes, as "balance metrics" or "metrics of balance of benefit and harm." Although the use of a balance metric represented an important development in making decision-maker value judgments more explicit, colposcopies per life-years gained has been criticized as a balance metric because it is not based on evidence on women's preferences regarding the benefits and harms of screening (16). Measures integrating women's preferences are desirable and coherent with a patient-centered approach. Although cost-effectiveness of screening is an important consideration, screening recommendations in Canada and

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the USA have been to date based heavily on assessments of the balance between benefits and harms of screening over its cost-effectiveness (4, 5). Many countries, including Canada, still use cytology-based screening and still require further evidence on harms and benefits of HPV testing before implementing HPV-based screening. Countries that have already implemented HPV-based screening are still learning and adjusting their practices to ensure optimal outcomes, and could also benefit from evidence on harms and benefits of HPV-based screening.

In this study, we used a decision model we have previously calibrated to the Canadian context (17) to examine different balance metrics to measure whether the benefits of cervical cancer screening outweigh its potential harms in unvaccinated women. We compared these metrics between cytology-based and HPV-based screening strategies to assess which strategies may lead to a better balance between benefits and harms. We solely considered health harms to the woman, and did not consider costs, as we focused on health outcomes for women participating in screening.

Materials and Methods

Model description

We used a previously developed state-transition (Markov) model of cervical cancer natural history and screening in R 3.5.3 (17). The model was calibrated to reproduce Canadian data on age-specific HPV infection prevalence, cervical intraepithelial neoplasia (CIN) prevalence, age-specific cervical cancer incidence, and HPV type distribution in cervical cancer before the introduction of HPV vaccination programs. A detailed description of the model's structure, parameters, development, calibration, and validation has previously been published (17).

The model simulates cohorts of women from age 10 to 100 years. Women are subject to background age-specific mortality and hysterectomy rates. Women acquire HPV infections at an age-specific rate. Persistent infections have a type-specific probability of progressing sequentially between CIN states 1 and 3. All CIN states can naturally regress to a persistent infection state, which can potentially be cleared or lead again to progression. Women with CIN3 may progress to cervical cancer at an age-specific rate. Cervical cancers may become symptomatic and be diagnosed outside of screening. Women diagnosed with cervical cancer have an excess cervical cancer mortality rate additional to their background mortality rate.

Screening strategies

We modeled the impact of each screening strategy over the lifetimes of a cohort of 100,000 unvaccinated women. Screening scenarios were compared with a counterfactual scenario of no screening to calculate screen-attributable outcomes. All screening parameter values may be found in Supplementary Table S1.

Cytology-based screening scenarios

We first modeled cytology-based screening assuming perfect adherence to current Canadian recommendations (4), where 100% of women get screened once every 3 years with cytology between ages 25 and 69 (**Fig. 1**). We also had imperfect adherence scenarios based on observed age-specific screening adherence in Canada, where 53% and 68% of women are screened at least once every 3 years between ages 20 and 69 (18). In imperfect adherence scenarios, some women screen more or less frequently than every 3 years (Supplementary Fig. S3). Colposcopy referral guidelines vary across Canada, with some provinces using repeat cytology to follow-up low-grade lesions, whereas others refer them directly to colposcopy. During calibration we based model colposcopy referrals on observed referral rates by lesion grade in British Columbia, where most low-grade lesions are referred for a repeat cytology (low colposcopy referral scenarios; ref. 19). However, as some other provinces (Ontario, Québec) and countries recommend directly

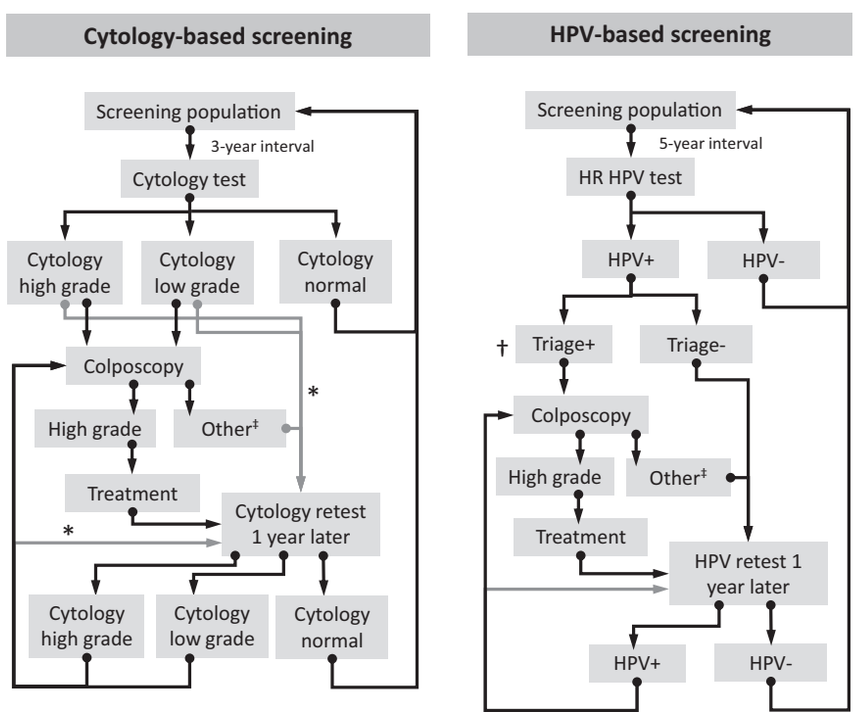

Figure 1.

Flowchart of cytology-based and HPV-based screening strategies. Mixed strategies use cytology-based screening in women aged <30 years and HPV-based screening in women aged ≥30 years. *High- and low-grade lesions may be immediately referred either to colposcopy or for retesting 1 year later, depending on scenario and age-specific probabilities. †A triage positive is a woman with an abnormal cytology test result (cytology triage scenarios), or a woman who is HPV16/18 positive and/or has an abnormal cytology test result (HPV16/18 and cytology triage scenarios). ‡Most low-grade lesions (CIN1) are recommended for repeat retesting; however, it is assumed a proportion would get eventually treated upon persistence. HPV, human papillomavirus; HR, high risk.

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referring low-grade lesions to colposcopy (20), we also examined scenarios where low-grade lesions have the same probability of being referred to colposcopy as high-grade lesions (high colposcopy referral scenarios). In all scenarios, women with abnormal cytology who are not referred to colposcopy were instead referred for cytology retesting one year later; those who retest abnormal again had a given age-specific probability of being referred to colposcopy (Supplementary Table S1), whereas those who retested normal returned to regular screening. Cytology testing had a 55% sensitivity and a 97% specificity for CIN2+ (9). Treatment of CIN was assumed to occasionally fail, with the lesion still being present in 14% and a persistent infection still being present in 15.8% of cases.

HPV-based screening scenarios

For HPV-based screening (**Fig. 1**), the screening test targeted 14 high-risk (HR) HPV types (HPV16/18/31/33/35/39/45/51/52/56/58/59/66/68) in combination. We assumed 5-year screening intervals (5, 21). In perfect adherence scenarios, 100% of women get screened once every 5 years from the age of 25 to either 60 or 70 years. For imperfect screening adherence scenarios, we rescaled the screening frequency so that the proportion of women having an HPV test every 5 years would be the same as the proportion of women having at least one cytology test in the past 3 years (Supplementary Fig. S3). HPV-positive women underwent a triage test; the sample for triage was assumed to be collected at the same time as the HPV test. We examined scenarios with cytology triage (abnormal cytology is considered triage positive), and scenarios with HPV-16/18 genotyping plus cytology triage (HPV16/18 positivity and/or abnormal cytology are considered triage positive). HPV-positive triage-positive women are referred to colposcopy, whereas HPV-positive triage-negative women are recommended a repeat HPV testing one year later. Women who retest HPV-positive one year later again have a given age-specific probability of being referred to colposcopy. We assumed the probability of adhering to colposcopy referrals for screen-positive results would be the same as in cytology-based screening scenarios with high colposcopy referral (Supplementary Table S1). Persistently HPV-positive women are retested at 1-year intervals and only reintegrate regular screening once they retest HPV negative. HR HPV testing was assumed to have 100% virological sensitivity and specificity to detect its 14 HR HPV types; its corresponding sensitivity and specificity to CIN2+ depended on HPV type distribution across parameter sets and was on average 94% (sensitivity) and 87% (specificity).

Mixed screening scenarios

We also examined scenarios where cytology-based screening was performed in women <30 years old, and HPV-based screening was performed in women ≥30 years old, similar to current US recommendations (5).

Analyses

We reported results as the average (minimum–maximum) predictions of 55 previously fitted parameter sets (17). All outcomes were undiscounted and were cumulated over the lifetime of the cohort to capture the lifetime effects of screening.

We reviewed the literature for preference values women have given screen-related health outcomes (**Table 1**; refs. 22–25). A rationale for the selected preference values is provided in the Supplementary Data. These preference values were used as weights to calculate quality-adjusted life-years (QALY) lost and gained with screening. QALY are a measure of the combined quality and quantity of life experienced, with 1 QALY corresponding to a year of perfect health, 0 corresponding to death, and values between 0 and 1 corresponding to outcomes leading to losses in quality of life.

Harm outcomes

We considered as health harms procedures and outcomes that could potentially cause psychological stress or physical injury to a woman: screening tests, positive test results, detection and management of lesions (triage, colposcopies, CIN diagnoses, treatments, and retesting), and QALY losses from these procedures. We counted as a "screening test" only the initial screening test; subsequent triage and follow-up tests were considered part of the management of screen-positive women. "Colposcopies" include all colposcopies a woman may experience from immediate referrals, follow-up of persistent HPV positives and persistent low-grade lesions, and follow-ups post-CIN treatment. The losses in QALY for management of screen-positive women are based on average trajectories of care that have been calculated for women based on their most severe diagnosis (normal, CIN1, CIN2, CIN3, cancer; ref. 23).

Benefit outcomes

We considered as screening benefits the prevented cervical cancers, prevented cervical cancer deaths, life-years gained from prevented deaths, and QALY gains from prevented cancer morbidity. Prevented cancers and deaths were estimated by comparing screening scenarios to a counterfactual scenario without screening.

Table 1. Preference values of health states used in analysis.

Event/health state	Value	Assumed 95% CI	Based on
Perfect health	1	—	—
Screening, negative result	0.9967	(0.9916–1)	Simonella 2014 (22)
Screening, abnormal cytology result	0.96	(0.95–0.97)	Insinga 2007 (23) and Sawaya 2019 (37)
Screening, HPV-positive result (equal preference scenarios)	0.96	(0.95–0.97)	—
Screening, HPV-positive result (lower preference scenarios)	0.94	(0.8544–1)	Howard 2008 (24) and Sawaya 2019 (37)
CIN1 diagnosis + management	0.89	(0.85–0.94)	Insinga 2007 (23)
CIN2 diagnosis + management	0.89	(0.83–0.96)	Insinga 2007 (23)
CIN3 diagnosis + management	0.89	(0.80–0.98)	Insinga 2007 (23)
Cervical cancer	0.67	(0.562–0.770)	Kuppermann 2010 (25)
Cancer remission	0.82	(0.8160–1)	Kuppermann 2010 (25)
Death	0	—	—

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

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Metrics of balance of benefits and harms

We cumulated harm and benefit outcomes over the cohort's lifetime to calculate various balance metrics. These balance metrics contrasted harms with benefits such as colposcopies per health outcome (e.g., colposcopies/life-year gained; refs. 12, 15) and number needed to screen (NNS) per health outcome. We also calculated a net benefit (26) of screening using the cumulative lifetime net QALY gain. The cumulative lifetime net QALY gain of a screening strategy was calculated as the difference between the cohort's total cumulative lifetime QALYs with that screening scenario and the cohort's total cumulative lifetime QALY in a counterfactual scenario without screening:

$$\sum \text{QALY}_{\text{net}} = \sum \text{QALY}_{\text{screening scenario}} - \sum \text{QALY}_{\text{no screening scenario}}$$

A positive net QALY gain indicates that the benefits of a screening strategy outweigh its harms, whereas a negative net QALY gain indicates harms outweigh benefits. Higher net QALY gains indicate a better balance of benefits and harms. Sample calculations for these balance metrics are provided in the Supplementary Appendix.

Balance of harms and benefits of screening by age

We used incremental net QALY gains to identify ages where HPV-based screening leads to more harms than benefits. We first identified the age at which one lifetime HPV screening test leads to the highest lifetime net QALY gain. We then used a forward selection process to add additional lifetime screens, selecting at each step the next age in 5-year intervals where screening led to the highest incremental net QALY gain. We continued the forward selection process until additional lifetime screens only decreased the lifetime net QALY gain (where more screening tests led to more harms than benefits).

Sensitivity analyses

Due to some women's opposition to longer screening intervals (27) or lack of organized screening in some settings, it is possible women might maintain the same screening intervals with HPV-based screening. We examined over-screening scenarios where women have the same 3-year age-specific probabilities of being screened with HPV-based screening as with cytology-based screening. Conversely, some health providers have expressed concern that screening adherence may decrease with HPV-based screening (28). We examined under-screening scenarios where current observed 3-year screening adherence would only be achieved every 7 years with HPV-based screening (instead of every 5 years). As over-screening and under-screening scenarios assume imperfect screening adherence, some women in these scenarios screen more or less frequently than every 3 and 7 years.

In main analyses, we assumed a positive HPV test result would cause the same quality-of-life loss as an abnormal cytology result (**Table 1**). However, in some studies, women report higher quality-of-life losses from knowing they are HPV positive, not realizing that an abnormal Pap smear is usually caused by an HPV infection (24, 25, 29, 30). We therefore included sensitivity analyses where a positive HPV test result would cause a greater quality-of-life loss than an abnormal cytology test result (lower test preference scenarios). To assess whether results were sensitive to how women value health outcomes, we also reran the model with resampled preference values from the confidence intervals in **Table 1**, using Latin Hypercube Sampling.

Validation

The model has been previously calibrated and validated with cytology-based screening. Briefly, the model predictions are based on 55 parameter sets that best reproduced cervical cancer incidence by age, HPV prevalence by age, CIN prevalence, and HPV type distribution in cancer in Canada based on the log-likelihood from a sample of 40,000 parameter sets (17). To validate model HPV-based screening predictions, we further cross-validated model outcomes against observed outcomes from Canadian screening registries and four HPV screening clinical trials from Canada, the USA, and the Netherlands (Supplementary Figs. S4–S7).

Results

Harms

Assuming perfect screening adherence, cytology-based screening with a high colposcopy referral between ages 25 and 70 was estimated to lead to 1,319,854 cytology screening tests, 30,395 colposcopies, and 4,826 QALY lost from screening procedures over the lifetimes of 100,000 women (**Table 2** and **Fig. 2**). Cytology-based screening was predicted to lead to fewer colposcopies when we assumed low-grade lesions are mainly managed through repeat cytology testing (low colposcopy referral scenario). HPV-based screening with cytology triage between ages 25 and 60 led to 698,250 HPV screening tests, 73,296 colposcopies, and 5,640 QALY lost from screening procedures. HPV16/18 genotyping plus cytology triage led to more colposcopies than cytology triage alone.

Benefits

Assuming perfect screening adherence, cytology-based screening with high colposcopy referral was estimated to prevent 1,774 cancers and 636 cancer deaths over the lifetimes of 100,000 women, leading to 13,504 life-years gained plus 2,056 QALY gained from prevented morbidity for a total of 15,560 QALY gained from prevented cancer morbidity and mortality (**Table 2**; **Fig. 2**). HPV-based screening between 25 and 60 years with cytology triage was estimated to prevent 1,967 cancers and 677 cancer deaths, leading to 15,066 life-years gained plus 2,264 QALY gained from prevented morbidity for a total of 17,330 QALY gained from prevented cancer morbidity and mortality. HPV16/18 genotyping plus cytology triage led to slightly more prevented cancers and cancer deaths than cytology triage alone.

Balance of benefits and harms

HPV-based screening strategies were predicted to have lower colposcopy efficiency than cytology-based strategies, requiring more colposcopies per prevented outcome (**Table 3**). For example, cytology-based screening with perfect screening adherence resulted in fewer colposcopies/life-year gained (2.3) than HPV-based screening with cytology triage (4.9). These low numbers were because a woman whose cervical cancer death is prevented would gain on average 21 life-years.

HPV-based screening strategies had a higher screen test efficiency than cytology-based screening, requiring fewer screening tests per prevented outcome. For example, cytology-based screening with high colposcopy referral resulted in screening 744 women per prevented cancer, whereas HPV-based screening with cytology triage between ages 25 and 60 years resulted in screening 355 women per prevented cancer.

All screening strategies were predicted to lead to a positive cumulative lifetime net QALY gain (**Table 3**), meaning that the expected benefits of cervical cancer screening substantially outweighed its harms over a lifetime. Due to the time lag between screening and cancer prevention, the harms from screening accrue earlier in life and the benefits from screening accrue later in life, as most screen-prevented cancers would have been diagnosed in middle age

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Table 2. Cumulative lifetime harms and benefits attributable to cervical cancer screening (compared with no screening) for a cohort of 100,000 women; average predictions of 55 parameter sets.

			Harms						Benefits				
Screening test	**Triage**	**Ages**	**Screening tests[a]**	**Positive screening tests[a]**	**Colpo-scopies[b]**	**CIN2/3 detected**	**CIN3 detected**	**Quality of life lost from screening procedures (QALY)[c]**	**Cancers prevented**	**Cancer deaths prevented**	**Cancer morbidity prevented (QALY)**	**Life-years gained**	**Total QALY gained[d]**
No screening (reference)			0	0	0	0	0	0	0	0	0	0	0
Perfect screening adherence[e]													
Cytology	Low colposcopy referral[f]	25–70 y	1,319,753	48,837	8,785	6,756	2,731	4,872	1,751	628	2,030	13,340	15,371
Cytology	High colposcopy referral[f]	25–70 y	1,319,854	48,460	30,395	6,474	2,633	4,826	1,774	636	2,056	13,504	15,560
Cytology (25) and HPV testing (≥30)	Cytology	25–60 y	698,936	51,455	60,580	6,565	2,166	4,769	1,923	671	2,220	14,728	16,948
Cytology (25) and HPV testing (≥30)	HPV16/18 and cytology	25–60 y	699,091	51,222	66,961	6,577	2,085	4,745	1,950	677	2,249	14,938	17,187
HPV testing	Cytology	25–60 y	698,250	68,507	73,296	6,537	1,889	5,640	1,967	677	2,264	15,066	17,330
HPV testing	HPV16/18 and cytology	25–60 y	698,435	68,206	84,756	6,526	1,773	5,608	1,995	684	2,294	15,285	17,579
Imperfect screening adherence[g]													
Cytology	Low colposcopy referral[f]	20–70 y	1,141,916	42,420	7,825	5,894	2,573	4,235	1,527	551	1,772	11,634	13,407
Cytology	High colposcopy referral[f]	20–70 y	1,142,092	42,121	27,012	5,675	2,490	4,199	1,556	562	1,806	11,849	13,654
Cytology (<30) and HPV testing (≥30)	Cytology	20–70 y	847,794	47,577	33,820	6,300	2,394	4,986	1,754	628	2,034	13,415	15,449
Cytology (<30) and HPV testing (≥30)	HPV16/18 and cytology	20–70 y	848,360	47,211	43,917	6,319	2,299	4,950	1,808	645	2,094	13,829	15,923
HPV testing	Cytology	25–70 y	676,391	52,007	41,146	6,167	2,338	5,050	1,751	628	2,031	13,380	15,411
HPV testing	HPV16/18 and cytology	25–70 y	677,121	51,525	56,125	6,155	2,194	5,001	1,813	645	2,099	13,856	15,955
HPV testing	Cytology	25–60 y	591,620	49,367	39,908	5,893	2,219	4,666	1,712	604	1,983	13,190	15,173
HPV testing	HPV16/18 and cytology	25–60 y	592,270	48,922	54,645	5,887	2,084	4,621	1,775	622	2,053	13,668	15,720
Imperfect screening adherence sensitivity analyses[h]													
HPV testing (over-screening)	Cytology	20–70 y	1,102,390	96,470	61,968	6,754	2,026	7,514	1,924	670	2,217	14,691	16,908
HPV testing (over-screening)	HPV16/18 and cytology	20–70 y	1,103,656	95,752	90,854	6,628	1,785	7,436	1,977	685	2,276	15,099	17,375
HPV testing (under-screening)	Cytology	25–60 y	437,699	38,893	32,747	5,385	2,223	4,037	1,560	558	1,813	12,021	13,833
HPV testing (under-screening)	HPV16/18 and cytology	25–60 y	438,110	38,547	44,551	5,426	2,137	4,005	1,629	579	1,889	12,548	14,437

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; QALY, quality-adjusted life-years.

[a]Includes only initial screening test; subsequent triage and follow-up tests are considered to be part of the management of screen-positive women. A positive screen test corresponds to an abnormal cytology test with cytology-based screening, or an HR HPV-positive test with HPV-based screening.

[b]Includes all colposcopies from immediate referrals, follow-up of persistent HPV positives and persistent low-grade lesions, and follow-up post-CIN treatment. A single woman may experience multiple colposcopies during her management, so the number of colposcopies may be higher than the number of women with positive screen tests.

[c]QALY losses from attending screening, receiving an abnormal result, follow-up, and management of lesions.

[d]Sum of cancer morbidity prevented and life-years gained from prevented cancers and cancer deaths. Does not include QALY losses from screening procedures.

[e]Perfect adherence: All women get screened exactly once every 3 years (cytology) or every 5 years (HPV testing).

[f]Cytology-based screening scenarios with low colposcopy referral assume high-grade lesions have an age-specific 65%–97% probability of being immediately referred to colposcopy whereas low-grade lesions have only a 3%–9% age-specific probability of being immediately referred to colposcopy. Cytology-based screening scenarios with high colposcopy referral assume all abnormal cytology tests have a 65%–97% age-specific probability of being immediately referred to colposcopy.

[g]Imperfect adherence: 53%–68% of women (depending on age) get screened at least once within a 3-year interval (cytology) or within a 5-year interval (HPV testing).

[h]Over-screening: 53%–68% of women (depending on age) get screened at least once within a 3-year interval, similar to the cytology-based imperfect screening scenario. Under-screening: 53%–68% of women (depending on age) get screened at least once within a 7-year interval.

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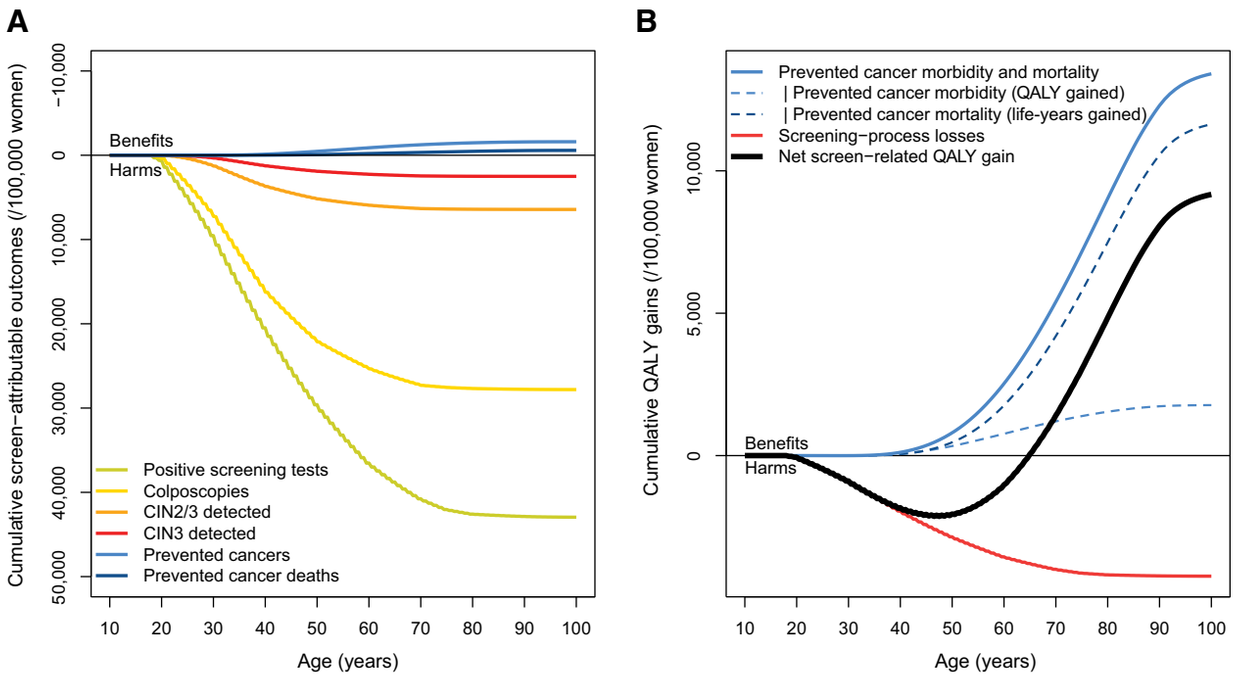

Figure 2.

Model-predicted lifetime cumulative screen-attributable health outcomes (**A**) and QALY lost and gained (**B**). Results are for a cohort of 100,000 women in the cytology-based screening with high colposcopy referral scenario (imperfect screening adherence). Results are the average of predictions from 55 parameter sets. CIN, cervical intraepithelial neoplasia; QALY, quality-adjusted life-years.

(**Fig. 2B**). Most QALY gains from screening were due to life-years gained from prevented cancer deaths (**Table 2**). The model predicted that HPV-based screening strategies would in most cases lead to higher average net QALY gains than comparable cytology-based screening strategies, due to more prevented cancer deaths.

Balance of harms and benefits of HPV-based screening by age

A single lifetime HPV screening test led to net lifetime QALY gains between the ages of 25 and 65 (**Fig. 3A**). Screening at age 70 years and above was predicted to lead to net QALY losses (more harms than benefits), even for women who had never screened before (**Fig. 3A**). The highest average net QALY gains were achieved by 5 lifetime screens with HPV-based screening, with the forward selection process favoring screening at ages 35, 45, 30, 55, and 50 (18% of parameter sets also favored a sixth lifetime screen at age 65; ref. **Fig. 3B**). The colposcopies per life-year gained of additional lifetime screens are shown in Supplementary Fig. S8. Although additional lifetime screens further reduced cervical cancer incidence (**Fig. 3C**), they were predicted to decrease the net lifetime QALY gain (cause more additional harms than additional benefits; ref. **Fig. 3B**). Screening at a given age was predicted to lead to slight increases in cancer incidence at that age due to earlier screen detection of preclinical cancers, but to substantial later decreases in incidence at older ages due to prevented cancers (**Fig. 3C**).

Sensitivity analyses

If women kept the same 3-year screening adherence with HPV-based screening as with cytology-based screening (over-screening scenarios), more cancers would be prevented (**Table 2**), but there would be substantially more screening harms, leading to a lower lifetime net QALY benefit than with 5-year intervals (**Table 3**). If instead screening adherence declines, and current 3-year screening adherence were only achieved every 7 years (under-screening scenarios), the model predicted that HPV-based screening would still lead to more prevented cancers than cytology-based screening (**Table 2**).

We ran the model with different resampled health state preference value sets (Supplementary Fig. S9). Whether cytology-based screening or HPV-based screening led to higher net QALY gains depended on the sample, and was most sensitive to the quality-of-life impact attributed to a positive HPV test result. HPV-based screening was more likely to be favored in resamples where a positive HPV test had a similar impact on quality of life as an abnormal cytology result (average preference 0.96 in samples favoring HPV-based screening), whereas cytology-based screening was more likely to be favored in resamples where a positive HPV test had a more negative impact on quality of life (average preference 0.92 in samples favoring cytology-based screening).

Discussion

In this modeling analysis, we assessed metrics of balance between benefits and harms of cervical cancer screening strategies in an unvaccinated population. HPV-based screening in unvaccinated women generally led to more prevented cancers, more colposcopies, and fewer screening tests over a lifetime than cytology-based screening. Consequently, balance metrics using colposcopies as the main harm outcome favored cytology-based screening, whereas balance metrics using screening tests as the main harm outcome favored HPV-based screening strategies. Many HPV-based screening strategies were predicted to have higher expected net lifetime QALY gains than cytology-based screening strategies due to more prevented cancers. Results were however sensitive to the assumed quality-of-

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Table 3. Metrics of balance of screening benefits and harms cumulated over a lifetime; average (minimum–maximum) predictions of 55 parameter sets.

			Net QALY gain		Colposcopies					Screening tests (NNS)				
Screening test	Triage	Ages	Equal HPV test preference[a]: per 100,000 women (years)	Lower HPV test preference[a]: per 100,000 women (years)	Per CIN2/3 detected	Per CIN3 detected	Per cancer prevented	Per cancer death prevented	Per life-year gained	Per CIN2/3 detected	Per CIN3 detected	Per cancer prevented	Per cancer death prevented	Per life-year gained
Perfect screening adherence[b]														
Cytology	Low colposcopy referral[c]	25–70 y	10,499 (4,719–17,663)	10,499 (4,719–17,663)	1.3 (1.2–1.6)	3.2 (1.9–6.6)	5 (4–9)	14 (11–29)	0.7 (0.5–1.1)	195 (103–386)	483 (214–868)	754 (511–1,240)	2,103 (1,350–3,606)	99 (67–161)
Cytology	High colposcopy referral[c]	25–70 y	10,735 (5,040–17,797)	10,735 (5,040–17,797)	4.7 (3.0–8.3)	11.5 (5.6–20.9)	17 (12–26)	48 (34–85)	2.3 (1.6–3.3)	204 (107–406)	501 (220–899)	744 (509–1,203)	2,076 (1,342–3,490)	98 (67–156)
Cytology (25) and HPV testing (≥30)	Cytology	25–60 y	12,179 (5,036–19,329)	11,618 (4,497–18,772)	9.2 (4.9–19.5)	28.0 (12.3–60.4)	32 (18–76)	90 (55–227)	4.1 (2.4–9.8)	106 (58–203)	323 (129–614)	363 (252–554)	1,042 (685–1,657)	47 (33–72)
Cytology (25) and HPV testing (≥30)	HPV16/18 and cytology	25–60 y	12,443 (5,316–19,590)	11,881 (4,777–19,032)	10.2 (5.3–21.1)	32.1 (13.9–69.0)	34 (20–81)	99 (61–243)	4.5 (2.6–10.4)	106 (58–203)	335 (131–647)	358 (250–542)	1,032 (681–1,629)	47 (33–70)
HPV testing	Cytology	25–60 y	11,690 (4,409–18,742)	10,790 (3,543–17,857)	11.2 (5.9–22.6)	38.8 (16.4–85.3)	37 (23–86)	108 (69–261)	4.9 (2.9–11.1)	107 (58–205)	370 (141–738)	355 (247–534)	1,031 (680–1,626)	46 (32–69)
HPV testing	HPV16/18 and cytology	25–60 y	11,971 (4,717–19,015)	11,070 (3,851–18,130)	13.0 (6.8–25.4)	47.8 (19.4–107.0)	42 (26–94)	124 (80–288)	5.5 (3.4–12.2)	107 (58–206)	394 (146–803)	350 (245–522)	1,022 (677–1,598)	46 (32–67)
Imperfect screening adherence[d]														
Cytology	Low colposcopy referral[c]	20–70 y	9,172 (3,822–16,061)	9,172 (3,822–16,061)	1.3 (1.2–1.7)	3.0 (1.9–5.9)	5 (4–9)	14 (11–30)	0.7 (0.5–1.2)	194 (100–389)	444 (203–757)	748 (490–1,287)	2,071 (1,291–3,744)	98 (64–166)
Cytology	High colposcopy referral[c]	20–70 y	9,455 (4,176–16,232)	9,455 (4,176–16,232)	4.8 (3.0–8.6)	10.8 (5.5–18.7)	17 (12–27)	48 (34–87)	2.3 (1.6–3.5)	201 (103–407)	459 (209–781)	734 (486–1,236)	2,033 (1,279–3,580)	96 (64–160)
Cytology (<30) and HPV testing (≥30)	Cytology	20–70 y	10,464 (3,686–17,466)	10,016 (3,255–17,020)	5.4 (3.0–11.5)	14.1 (6.8–30.9)	19 (12–47)	54 (34–137)	2.5 (1.5–6.1)	135 (71–256)	354 (151–622)	483 (326–764)	1,349 (868–2,214)	63 (43–99)
Cytology (<30) and HPV testing (≥30)	HPV16/18 and cytology	20–70 y	10,973 (4,219–17,996)	10,525 (3,788–17,549)	7.0 (3.7–14.7)	19.1 (9.1–43.2)	24 (14–58)	68 (42–169)	3.2 (1.8–7.5)	134 (71–257)	369 (155–653)	469 (321–728)	1,316 (854–2,120)	61 (42–94)
HPV testing	Cytology	25–70 y	10,361 (3,515–17,260)	9,711 (2,888–16,617)	6.7 (3.7–14.0)	17.6 (8.4–38.1)	24 (14–56)	66 (42–163)	3.1 (1.8–7.3)	110 (58–208)	289 (123–505)	386 (260–606)	1,078 (693–1,755)	51 (34–78)
HPV testing	HPV16/18 and cytology	25–70 y	10,954 (4,136–17,875)	10,303 (3,508–17,232)	9.1 (4.8–18.5)	25.6 (11.9–56.4)	31 (19–71)	87 (55–206)	4.1 (2.4–9.2)	110 (58–209)	309 (128–544)	374 (255–574)	1,050 (681–1,675)	49 (33–74)
HPV testing	Cytology	25–60 y	10,508 (3,809–17,313)	9,886 (3,211–16,699)	6.8 (3.7–14.2)	18.0 (8.6–39.3)	23 (14–56)	66 (42–167)	3.0 (1.8–7.1)	100 (53–192)	267 (113–466)	346 (231–548)	980 (622–1,634)	45 (30–70)
HPV testing	HPV16/18 and cytology	25–60 y	11,099 (4,421–17,934)	10,476 (3,821–17,319)	9.3 (4.8–18.8)	26.2 (12.2–58.3)	31 (19–70)	88 (55–211)	4.0 (2.4–9.0)	101 (53–193)	284 (117–501)	334 (226–518)	952 (611–1,552)	43 (29–66)
Imperfect screening adherence sensitivity analyses[e]														
HPV testing over-screening	Cytology	20–70 y	9,395 (1,955–16,448)	7,970 (575–15,048)	9.2 (5.1–17.3)	30.6 (13.5–63.5)	32 (21–71)	92 (62–212)	4.2 (2.7–9.2)	163 (89–310)	544 (217–1,038)	573 (395–866)	1,644 (1,077–2,594)	75 (52–112)
HPV testing over-screening	HPV16/18 and cytology	20–70 y	9,939 (2,600–16,976)	8,513 (1,218–15,573)	13.7 (7.4–26.8)	50.9 (21.2–107.6)	46 (30–94)	133 (90–284)	6.0 (3.9–12.3)	167 (91–319)	618 (234–1,198)	558 (390–829)	1,611 (1,065–2,494)	73 (51–108)
HPV testing under-screening	Cytology	25–60 y	9,796 (3,601–16,379)	9,329 (3,151–15,922)	6.1 (3.3–13.2)	14.7 (7.3–33.2)	21 (13–51)	59 (37–151)	2.7 (1.6–6.6)	81 (42–156)	197 (86–330)	281 (184–457)	784 (491–1,343)	36 (24–58)
HPV testing under-screening	HPV16/18 and cytology	25–60 y	10,433 (4,205–16,998)	9,965 (3,754–16,541)	8.2 (4.3–17.3)	20.8 (10.1–47.9)	27 (16–64)	77 (48–190)	3.6 (2.1–8.2)	81 (42–155)	205 (88–346)	269 (179–429)	756 (479–1,266)	35 (23–55)

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; NNS, number needed to screen; QALY, quality-adjusted life-years.

[a]Lower HPV test preference assumes women have higher QALY losses from a positive HPV test than an abnormal cytology test result (**Table 1**). Equal test preference assumes women have the same QALY loss from a positive HPV as an abnormal cytology test result.

[b]All women get screened exactly once every 3 years (cytology-based screening) or every 5 years (HPV-based screening).

[c]Cytology-based screening scenarios with low colposcopy referral assume high-grade lesions have an age-specific 65%–97% probability of being immediately referred to colposcopy, whereas low-grade lesions have only a 3%–9% age-specific probability of being immediately referred to colposcopy. Cytology-based screening scenarios with high colposcopy referral assume all abnormal cytology tests have a 65%–97% age-specific probability of being immediately referred to colposcopy.

[d]Assumes 53%–68% of women (depending on age) get screened within a 3-year interval (cytology-based screening) or within a 5-year interval (HPV-based screening).

[e]Over-screening: 53%–68% of women (depending on age) get screened at least once within a 3-year interval, similar to the cytology-based imperfect screening scenario. Under-screening: 53%–68% of women (depending on age) get screened at least once within a 7-year interval.

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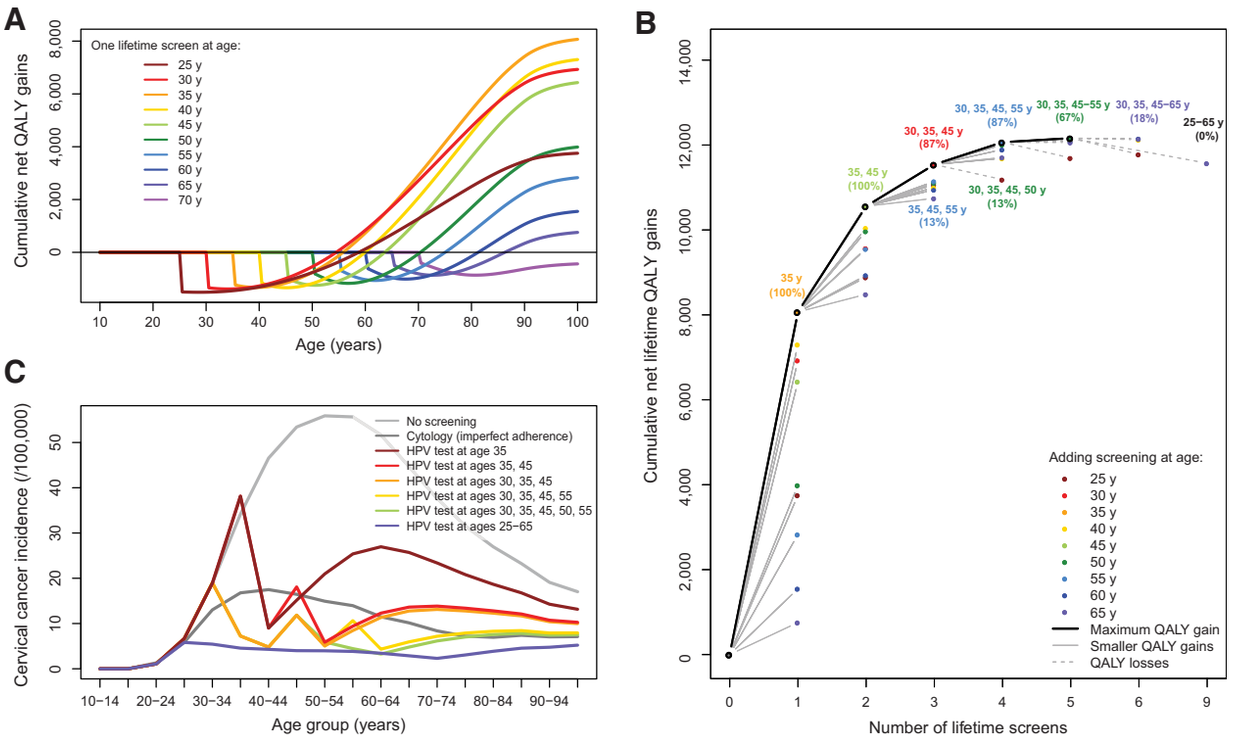

Figure 3.

Cumulative lifetime net QALY gain and cervical cancer incidence by age and by number of lifetime screens. **A,** Cumulative net QALY gain for a single lifetime screen by age. **B,** Cumulative lifetime net QALY gain by the number of lifetime screens. **C,** Cervical cancer incidence rates by age. Results are the average of predictions from 55 parameter sets. Results are for scenarios with perfect adherence to HPV-based screening (cytology triage). In **B**, the percentages between parentheses indicate the proportion of parameter sets that selected that age as maximizing the cumulative net QALY gains in the forward selection process. Peaks in cancer incidence in **C** are due to all women screening at a given age, causing increases in screen-detected cancers in that age group. HPV, human papillomavirus; QALY, quality-adjusted life-years.

life loss caused by a positive HPV test and the follow-up management strategy for abnormal tests.

Evidence-based cancer screening recommendations are based on literature reviews of the expected health benefits and harms of screening (4, 5, 14, 31). The use of balance metrics to contrast benefits and harms would help make value judgments more quantitative and transparent. However, balance metrics have been relatively little used to date in cancer screening decision-making. To our knowledge, the USPSTF are the first to recommend an explicit balance metric (colposcopies/life-year gained) in decision models to evaluate the balance of benefits and harms of cervical cancer screening strategies (12, 15).

Balance metrics based on clinical outcomes (e.g., colposcopies/life-year gained) may be easier to understand for decision-makers and clinicians, who may have experience with these outcomes. However, (i) a single outcome such as colposcopies does not capture all potential harms; (ii) there is no established threshold for what constitutes an acceptable tradeoff (i.e., how many colposcopies are worth one life-year); and (iii) they reflect the policy-makers' value judgment, and not necessarily the screened women's value judgments regarding their preferred health outcomes (16). The net QALY gain has several advantages: (i) it captures screening's positive and negative effects on both morbidity and mortality; (ii) there is an unambiguous threshold (>0) where benefits outweigh harms; and (iii) preference weights elicited from screen-eligible women allow integrating patient preferences in the decision process. However, the methods for eliciting health preferences may be subject to bias, and can yield different results with different methods and with different populations depending on their experience with screening outcomes (32). Although net QALY gains are not yet widespread as a balance metric, they were notably used by the USPSTF to analyze the balance of benefits and harms of preventive aspirin use (33).

Most previous modeling studies have focused on the cost-effectiveness of screening strategies (34–37). The metrics used in health economic analyses [generally the incremental cost-effectiveness ratio (ICER)] are metrics that evaluate value for money, not the balance between benefits and harms. Therefore, the most cost-effective screening strategies (e.g., the best ICER) may not necessarily be those that maximize the balance of health benefits and harms. Although cost-effectiveness is an important consideration for policy-makers, patients may be more amenable to changes in screening recommendations when they are framed instead in terms of the balance of harms and benefits (e.g., more screening will lead to unnecessary tests that will not help them live longer; refs. 38, 39). Opposition to HPV-based screening in some countries stems from a perception that increasing screening intervals and reducing screen-eligible ages are decisions driven by cost-cutting considerations that put women's health at risk (27, 40). Our study and others (41, 42) suggest instead that longer 5-year intervals with HPV-based screening are safe and necessary in order to improve the balance of benefits and harms of screening. Although this might be more easily realized in an

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organized screening setting, evidence suggests that in nonorganized settings women do change their screening intervals after changes in recommendations (43). Acceptance of longer screening intervals has also increased over time (44).

Most cervical cancer screening models have predicted that HPV-based screening in unvaccinated women would likely prevent a similar or higher number of cervical cancers than cytology-based screening (12, 37, 41, 45–48). However, only a few studies have yet included explicit metrics of balance of benefits and harms (12, 41, 47). Our model predicted a similar number of colposcopies per life-year gained with cytology-based screening (2.3) to Kim and colleagues (3.0; ref. 12) when we assumed a high colposcopy referral rate of low-grade lesions, which is the recommended management strategy in the USA (20). To our knowledge, only Naber and colleagues used net QALY benefits specifically as a balance metric to compare cervical cancer screening strategies in a model adapted to the Netherlands, where screening is recommended every 5 years (41). They predicted the net QALY benefit would be higher with 5-year interval HPV-based screening than with 5-year interval cytology-based screening, but that women who keep screening at ≤3-year intervals would mostly have negative net QALY gains from adopting HPV-based screening. This result is concordant with our sensitivity analysis, which predicted that net QALY gains will be lower if women maintain the same screening intervals with HPV testing as they do with current 3-year screening guidelines in Canada. Results from both models suggest that 3-year intervals may not be appropriate for HPV-based screening, and that longer 5-year intervals would prevent just as many cancers while improving the balance of benefits and harms of HPV-based screening compared with cytology-based screening.

The main limitation of our analysis is the Markov structure of the model, which cannot remember a woman's screening results history, and consequently uses a simplified management algorithm for screening (**Fig. 1**). We assumed with HPV-based screening that women would stay under follow-up until they are HPV-negative. This mainly affected the colposcopy predictions; the large difference in colposcopies between cytology- and HPV-based screening predicted by the model was not from the immediate referral of triage-positive women, which was roughly comparable between strategies (Supplementary Fig. S6). The difference is because the model predicted there would be many women potentially requiring delayed colposcopy referrals due to persistent HPV infections at follow-up retests, and during post-CIN treatment follow-up. We chose this algorithm because repeat HPV testing or cotesting is the recommended management strategy in the USA (20), Australia (14), the UK (49), and most European countries that are implementing HPV testing (50). However, there are countries that use instead repeat cytology testing (Netherlands) or which do not retest HPV-positive triage-negative women (Sweden); these strategies are expected to lead to lower colposcopy referrals. Our results therefore overestimate the number of colposcopies that would occur in these countries without HPV retesting, or if countries decide to limit the number of repeat retests that HPV-positive women undergo. Nevertheless, our results are consistent with most other decision models that have predicted that HPV-based screening in unvaccinated women would likely lead to substantially more colposcopies than cytology-based screening (12, 37, 41, 45–47) and in some cases more than double (12). In England and Australia, colposcopy referrals increased by approximately 80% (51) to 300% (52) after implementing HPV testing using a similar algorithm to the one we model. Therefore, though the model likely overestimates the number of colposcopies due to structural limitations of Markov models, much evidence supports that the number of colposcopy referrals is likely to increase with HPV testing.

Our main objective was to illustrate a more systematic method for evaluating the balance of benefits and harms that can be applied in different contexts. The quantitative results for balance metrics and number of benefit and harm outcomes are likely to be different in other countries due to differences in screening performance and implementation; however, the consistency of our model predictions from those of other countries suggests that the qualitative insights are likely to be applicable to many high-income countries with similar screening recommendations. Our results are however not likely to be applicable to low-income countries due to differences in screening modalities and life expectancy, which influence the harms and benefits of screening.

We assumed in the main analysis that a positive HPV test would have the same impact on quality of life as an abnormal cytology test, and in all these scenarios, the net QALY gains were higher with HPV-based screening than with cytology-based screening. Nonetheless, studies have shown some women react more negatively to a positive HPV test (24, 25, 29, 30). We therefore included sensitivity analyses assuming women would find a positive HPV test more distressing, in order to provide more conservative estimates of net benefit for HPV-based screening. However, it has become common practice with cytology screening to explain to women that cervical abnormalities are caused by infection with HPV. It is therefore likely that as public awareness of HPV increases, the quality-of-life impacts of positive HPV and cytology tests will tend to converge. Nevertheless, our results highlight the importance of developing sensitive communication strategies for informing women of a positive HPV test in order not to increase the harms of cervical cancer screening.

The primary ethical imperative of screening is to cause more benefits than harms (3). Our aim with this analysis was to contribute to the wider discussion on how to assess this balance of harms and benefits of population-level interventions in order to better achieve this goal (26). However, other issues such as cost-effectiveness and feasibility also influence screening policy decisions, and the screening strategy that offers the best balance of health benefits and harms may not necessarily be the most cost-effective, the most feasible, nor the one that prevents the most cancers. We only modeled unvaccinated women; the balance of benefits and harms will likely change over time and will need to be reevaluated as HPV-vaccinated cohorts have aged into the screening population. Including metrics of balance of benefits and harms in decision-making is coherent with establishing benchmark risk thresholds to make screening guidelines more consistent and transparent.

Disclosure of Potential Conflicts of Interest

W.H. Gotlieb is an advisory board member for AstraZeneca. E.L. Franco served as occasional advisor to Merck, GlaxoSmithKline, and Roche in the past. His institution received grants in the past from Merck and Roche in support of research that he led. He has also applied for a patent on methylation markers for cervical cancer screening. No potential conflicts of interest were disclosed by the other authors.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E.L. Franco

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