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Using simulation-optimization to construct screening strategies for cervical cancer

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Abstract Cervical cancer is the second most common cancer in women worldwide. Cervical screening is critical for preventing this type of cancer. Traditionally, screening strategies are evaluated from an economic point of view through cost-effectiveness analysis. However, cost-effectiveness analysis is typically performed on a limited number of de facto or predetermined screening policies. We develop a simulation-optimization model to determine the ages at which screening should be performed, resulting in dynamic, age-based screening policies. We consider three performance measures: cervical cancer incidence, the number of cervical cancer deaths, and the number of life years lost due to cervical cancer death. Using each performance measure, we compare our optimal, dynamic screening strategies to standard policies considered in the health screening literature that are static and predetermined. We also evaluate the anticipated impact of vaccinations for preventing cervical cancer. The strategies that are developed are compared to those used in practice or considered in the literature. The Centers for Disease Control and Prevention recommends one screening every 3 years, resulting in 14 scheduled lifetime screenings. Our dynamic screening strategies provide approximately the same health benefits as this but with four to six fewer scheduled screenings, depending on the performance measure considered. Our dynamic strategies also provide approximately the same health benefits as screening every 2 years, but with six to nine fewer scheduled screenings. The results suggest that dynamic, age-based cervical cancer screening policies offer substantial economic savings in order to offer the same health benefits as equally spaced screening strategies.

Keywords Simulation-optimization · Health care policy · Preventive medicine · Women's health · Vaccination

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1 Introduction

Cervical cancer is the second most common cancer in women worldwide. The National Cancer Institute [1] estimates that 11,150 women were diagnosed with cervical cancer in 2007 in the US, of whom 3,650 died. Recent research has shown that the human papillomavirus (HPV) is the only cause of cervical cancer. An estimated 6.2 million US women get a new HPV infection every year, adding up to approximately 20 million women who have an HPV infection at any given time [2]. By the age of 50, it is estimated that at least 80% of women will have had an HPV infection [3]. Cervical cancer is often asymptomatic until it is in its advanced stages. Therefore, it has become the focus of intense screening, primarily through Papanicolaou (Pap) smears. Screening aims to detect abnormal cells in the cervix before they develop into cancer. Treating these pre-cancerous abnormal cells is the primary mechanism for preventing cervical cancer from developing. In the absence of screening programs, it is estimated that more than 95% of HPV infections would regress naturally (rather than develop into cancer) and that 3.1–3.4% of women would develop cervical cancer [4].

Due to the central role of screening towards preventing cervical cancer, developing methods to maximize the effect of screening strategies are critical. In this paper, we focus on identifying how to schedule dynamic, age-based screenings in ways that prevent cervical cancer incidence and

improve quality of life in a cost-effective manner. These screening strategies are dynamic in that the time between screenings are not necessarily equally spaced (e.g., every 3 years), but rather the time between screenings changes with the age of the patient. We present a simulation-optimization model that captures a natural history of cervical carcinogenesis in order to construct these dynamic screening strategies. At present, nearly all mathematical models for cervical cancer screening only assess the cost-effectiveness of predetermined, static screening strategies. Our key contribution is a methodology for identifying dynamic screening policies using optimization when considering a detailed model for the natural history of cervical carcinogenesis. We also evaluate how these dynamic screening strategies change for women who have received a vaccination that protects against HPV (and ultimately cervical cancer). The results suggest that the timing of screenings does not significantly change between vaccinated and unvaccinated women, even when the HPV vaccine does not offer lifetime protection.

1.1 Cervical cancer background

There are more than 100 types, or strains, of HPV. Only some of these strains cause cervical cancer. Although an oncogenic HPV infection is a necessary factor for developing cervical cancer, the immune system naturally eliminates most HPV infections. An HPV infection can progress to precancerous abnormal cells, called cervical intraepithelial neoplasia (CIN). There are three levels of CIN. Each level refers to the thickness of the skin covering the affected cervix: CIN I refers to mild cell changes; CIN II refers to moderate cell changes; CIN III refers to severe cell changes. Within each of these stages the disease may progress to the next state, or the immune system may naturally eliminate it (i.e., it regresses). Regression is more common; however, the chance of the immune system eliminating the disease is effectively zero once the HPV infection reaches cancerous levels. Cervical cancer has four stages denoted by FIGO I–IV (Fédération Internationale de Gynécologie et d'Obstétrique). These stages indicate how far the cancer has spread, where FIGO IV represents the most severe and invasive form of cervical cancer. Strictly speaking, one is said to have cancer in FIGO I–IV states and to have precancerous abnormal cells in CIN I–III states.

Precancerous abnormal cells and early stages of cervical cancer are often asymptomatic, which is why cervical cancer has been the focus of intense screening for prevention. The most widely used method of screening for cervical cancer is the Pap smear. The Centers for Disease Control and Prevention (CDC) provide general guidelines for Pap smears in the United States. Women are advised to start screening either at age 21 or 3 years after becoming sexually active, whichever occurs first. Women between the ages of 65 and 70 may stop having screenings after consulting with their doctor if they have not had three abnormal screenings and no abnormal screenings in 10 years. Women who have had a total benign hysterectomy do not need screening [1]. Screening methods such as Pap smears have associated costs, specificity levels, and sensitivity levels.

Recently, vaccines that prevent specific high risk HPV strains have been developed. Currently there are two such vaccines available, Gardasil (Merck) and Cervarix (Glaxo SmithKline). Both vaccines prevent infection of high risk HPV types 16 and 18, which account for about 70% of all cervical cancers [3]. Note that Gardasil also prevents HPV types 6 and 11, which cause about 90% of genital wart cases [1]. The CDC currently recommend that girls age 11–12 receive the HPV vaccine [5]. Because the vaccines are recent developments, there is little to no empirical information about the cost-effectiveness of the vaccines either by themselves or in conjunction with screening. This introduces additional uncertainties associated with assessing the transmission of HPV in immunized women, which makes it difficult to project the costs and benefits of HPV immunization [6, 7]. This research addresses this need by evaluating the potential impact of HPV immunization on the timing of cervical cancer screening.

1.2 Literature review

A review of the literature indicates that several mathematical models have been applied to study clinical interventions for cervical cancer. Some studies focused solely on constructing a model that accurately portrays the natural history of cervical cancer. Myers et al. [8] construct a nineteen-state non-stationary Markov model of a cohort of women from ages 15 to 85. They conduct sensitivity analysis by varying the parameters of the model to evaluate the effects of the changes on CIN I–III prevalence and cervical cancer incidence. Their key conclusion is that cancer incidence is most sensitive to the incidence of HPV and the probability of progression from CIN to cancer.

Some studies focus on analyzing the type-specific natural history of HPV due to the recent understanding that oncogenic HPV strains cause cervical cancer. They also consider the projected effects of new HPV-16/18 vaccines. Goldie et al. [6] construct a Markov model that partitions the HPV types to analyze the impact of such a vaccine. The HPV types are partitioned into non-oncogenic HPV, oncogenic 16/18 HPV, and oncogenic non-16/18 HPV. They include appropriate age-specific progression and regression parameters for the specific HPV types. Goldie et al. [6] conclude that a vaccine that protects against strains 16 and 18 is 98% effective in preventing cervical cancer

due to these strains, which prevents 51% of cancer overall. Kohli et al. [9] estimate the long-term impact of a HPV vaccine in the United Kingdom. They incorporate partial protection against oncogenic strains 31 and 45 from a vaccine designed to protect against strains 16 and 18. Their model predicts that the vaccine would result in a 66% reduction in precancerous lesions and a 76% reduction in both cervical cancer incidence and death. Neither model has evaluated the beneficial effects of HPV vaccination due to herd immunity (i.e., the reduction in the prevalence of HPV due to widespread immunization).

Ever since the wide application of organized screening programs, the incidence and mortality of cervical cancer have decreased dramatically in developed countries. However, in less-developed countries, cervical cancer is still a leading cause of cancer death in women. Goldie et al. [10] consider alternative cost-effective screening strategies for less-developed countries —South Africa, in this case— taking into consideration the limited resources available. Due to reduced resources and compliance levels in low-resource settings, Goldie et al. [10] conclude that HPV-DNA or visual inspection screening strategies that eliminate multiple visits can offer cost-effective alternatives to cytology-based (Pap smear) screening. In another similar study that considers the cost-effectiveness of cervical cancer in five developing countries, Goldie et al. [11] conclude that screening women once in their lifetime with visual inspection reduces the lifetime risk of cervical cancer by 25–36% and that screening women twice in their lifetime reduces the relative lifetime risk of cervical cancer by 40%.

Gustafsson and Adami [12] examine dynamic screening policies for understanding the relationship between a screening program and the natural history of cervical cancer. Similar to this paper, they consider the three objectives of minimizing cancer incidence, cancer deaths, and life years lost. However, they use a differential equation model of the natural history (a continuous-time model rather than using simulation-optimization). Their simpler model aggregates all of the precancerous stages as well as all of the undiagnosed and diagnosed cancer stages into three states (compared to eleven states in our model). In addition, they combine the sensitivity of screening tests, attendance, and compliance such that the model implicitly assumes that every woman and every screening is independent. As a result, the model by [12] cannot be generalized to consider that women having different probabilities of attending different screenings. While not the focus of this paper, the simulation model presented here can be used to identify screening policies that reflect different rates in individual patients attending screenings and complying with treatment rather than by making decisions on the aggregate level.

Cervical cancer incidence and mortality have greatly decreased in places where organized screening strategies are present. Several papers focus on comparing alternative screening intervals as well as various starting and ending ages in settings where organized screening exists. Siebert et al. [13] develop a non-stationary Markov model that depicts the natural history of cervical carcinogenesis in Germany. They consider cancer incidence, cancer death, and life years saved (LYS) and vary the screening interval from every year to 2, 3, or 5 years between screenings. They assume that screening starts at age 20 and stops at 85. They conclude that the most cost-effective screening interval is every 2 years. Mandelblatt et al. [14] also consider screening strategies in places with organized screening strategies. They develop a seventeen-state Markov model to estimate the expected costs and expected quality-adjusted life years (QALY) gained for 18 different screening strategies. The strategies are compared by considering three possible endpoints for screening (65, 75, and death), three possible screening strategies (Pap smear, HPV DNA testing, or both), and two possible screening intervals (every two and every 3 years). They conclude that screening with combined HPV and Pap smear testing every 2 years up to 75 captures 97.8% of the health benefits of screening until death. Therefore, considering different age limits is a cost-effective option to reduce the costs of screening strategies while maintaining the benefits.

Several other papers use Markov process models and simulation for identifying dynamic screening policies for other diseases. Harper and Jones [15] and Roberts et al. [16] develop a detailed simulation model for colorectal cancer that focuses on cancer event relationships and could be applied to other forms of cancer or disease. Evenden et al. [17] examine screening for Chlamydia using simulation that takes high-risk subgroups and their geographic dynamics into account, which results in a more holistic screening Chlamydia framework. Faissol et al. [18] develop a Markov decision process model to identify dynamic, risk-based screening policies for Hepatitis C. They take high-risk subgroups into account in order to establish who should be screened. Maillart et al. [19] introduce a partially observable Markov chain model to evaluate dynamic breast cancer screening policies in order to identify efficient, robust policies. Ozekici and Pliska [20] examine the impact of Type I and Type II errors on breast cancer screening policies. Güneş et al. [21] examine the impact of screening quality, centralization, and outreach on breast cancer screening quality. Brailsford et al. [22] develop a simulation model for the early detection of retinopathy in patients with diabetes, which evaluates the incidence and life years lost in patients based on the screening policies.

Other papers consider the sub-optimality of equally spaced screenings. Kirch and Klein [23] provide an

analytical model for determining the frequency of screenings. They show that the interval between screenings is approximately proportional to the square-root of the age-specific incidence probability of the disease. Zelen [24] develops an analytical model for determining the timing of screenings. Zelen [24] finds that screenings are equally spaced when the disease incidence is independent of time and when the sojourn time from pre-clinical to clinical disease states is exponentially distributed (except for the first and last screenings). The methodologies in all of these papers could be used to identify dynamic screening policies for a broad range of diseases.

Much of the previous work in this area has analyzed static screening policies for cervical cancer using a single objective function or has identified dynamic screening strategies for other diseases and conditions. In contrast to previous work in the area, this paper uses simulation-optimization to identify age-based, dynamic screening policies for cervical cancer that considers three objectives functions. In addition, this paper evaluates the anticipated impact of vaccinations for preventing cervical cancer in order to shed light on how the screening policies may change with respect variations in the duration of sustained vaccine immunity.

1.3 Objective

Studies of cervical cancer screening strategies consider only a limited number of predetermined strategies. Mandelblatt et al. [14] consider 42 different scenarios, but these 42 scenarios are a fraction of all the possible scenarios that could be considered, considering the age-dependent risks associated with cervical intraepithelial neoplasia (CIN) and cervical cancer. This implies that varying the screening intervals would provide more cost-effective strategies.

The importance of the ages at which screenings are performed has been noted in the literature. For example, Mandelblatt et al. [14] notice that stopping screening at 75 instead of screening until death captures 97.8% of the health benefits. Goldie et al. [11] predicts that screening women once in their lifetime at age 35 can reduce cervical cancer incidence by 25–36%. However, they did not take advantage of the full potential of optimally timing screenings through optimization, since they only considered a small number of predetermined screening strategies.

At present, simulation has not been used to construct dynamic cost-effective screening strategies to prevent cervical cancer. Simulation models are typically used to compare existing screening strategies, such as screening every 2, 3, and 5 years. Some intuition and experience about the natural history of cervical carcinogenesis is used to consider different start and end ages for screening, and to find the best age to screen if one screening is available in a woman's lifetime. In this paper, we simulate the natural history of cervical carcinogenesis. We then apply simulation-optimization methods to construct dynamic cost-effective screening strategies to compare these performance measures. Such strategies are more cost-effective than strategies used in practice or considered in the literature thus far. The goal of this study is to demonstrate that simulation-optimization can be used to identify dynamic screening strategies. These identified strategies are non-dominated when comparing health benefits and costs.

The medical literature defines health benefits in multiple ways. We consider three objectives for capturing health benefits: (1) cancer incidence, (2) cancer deaths, and (3) the life years saved in the screened population. We consider single objective simulation-optimization models, since medical screening models are typically evaluated according to a single objective [25, 26]. However, we retrospectively analyze the tradeoffs between the three objectives to show that it is possible to identify screening policies that simultaneously maximize all three objectives. When dealing with any type of clinical intervention, the most common comparison method is cost-effectiveness analysis. Note that the direct and indirect costs of cervical cancer screening are proportional to the number of screenings that are performed [27]. Thus, we use the number of available lifetime screenings as a proxy for costs. We specify how many lifetime screenings are available per woman (e.g., from 1 to 22) and then optimize the health benefits across a fixed number of screenings. The resulting solutions are screening strategies comprised of a set of ages when screening should occur to offer the best health benefits possible. However, we acknowledge that the number of scheduled lifetime screenings do not capture all of the costs, since treatment costs depend on how early cancer is identified. Such costs are not explicitly considered in this paper.

This paper is organized as follows. Section 2 provides a full description of the model that was constructed to simulate the natural history of cervical carcinogenesis as well as the formulation of the optimization models used to construct the screening strategies. Section 3 focuses on the analysis of the strategies given by the simulation-optimization model. Section 4 analyzes the impact of the HPV vaccine on the simulation-optimization model. Section 5 discusses overall conclusions and recommendations for further study.

2 The cervical cancer simulation model

This section provides a full description of the simulation model developed. First, we describe the general logical structure and assumptions of the model along with the

parameters used. Then, we discuss the verification and validation of the model. Finally, we discuss the formulation of the optimization models.

The goal of this study is to demonstrate how to construct dynamic cervical cancer screening strategies by using simulation-optimization. This is examined by maximizing the health benefits subject to the number of available lifetime screenings per woman in the screened population. In order to demonstrate this, a set of parameters that describe the natural history of cervical carcinogenesis are required to serve as the foundation on which we perform the analysis. We performed a systematic literature review to identify a model with the clearest and complete set of parameters that describe the natural history of cervical carcinogenesis. The model developed by Siebert et al. [13] captures the natural history of cervical carcinogenesis in Germany. The natural history of cervical carcinogenesis is very similar among Western European countries and the United States [13], and therefore, this model is an appropriate template.

2.1 General logical structure, assumptions, and parameters of the model

The cervical cancer simulation model is comprised of two sub-models. The first sub-model simulates the natural history of cervical carcinogenesis. The second simulates screening and treatment imposed by clinical interventions. The natural history sub-model is a sixteen-state discrete-time Markov process, simulated for a hypothetical cohort of 100,000 women between 15 and 85 years old. In such a cohort, all women are initially 15 years old and are assumed to be in the well state [27]. Each women moves through the simulation until they end in one of the four absorbing states. Figure 1 provides a graphical representation of the Markov process. The squares represent the health states and the arrows represent the possible transitions between the states over a Markov cycle of 1 year. Each possible transition in the model has a set of age-specific transition probabilities.

The 16 states of the model, along with their possible transitions between states are as follows:

1. Well: There are no cell changes on the skin of the cervix.

From this state, a woman can remain in the same state, progress to CIN I (i.e., an HPV infection), move to benign hysterectomy, or die from some cause other than cervical cancer.

2. CIN I: Mild cell changes on the skin of the cervix (a precancerous state).

From this state, a woman can remain in the same state, regress to well (naturally or upon successful treatment following a true positive test result), progress to CIN II, move to benign hysterectomy, or die from some cause other than cervical cancer.

3. CIN II: Moderate cell changes on the skin of the cervix (a precancerous state).

From this state, a woman can remain in the same state, regress to well (naturally or upon successful treatment following a true positive test result), progress to CIN III, move to benign hysterectomy, or die from some cause other than cervical cancer.

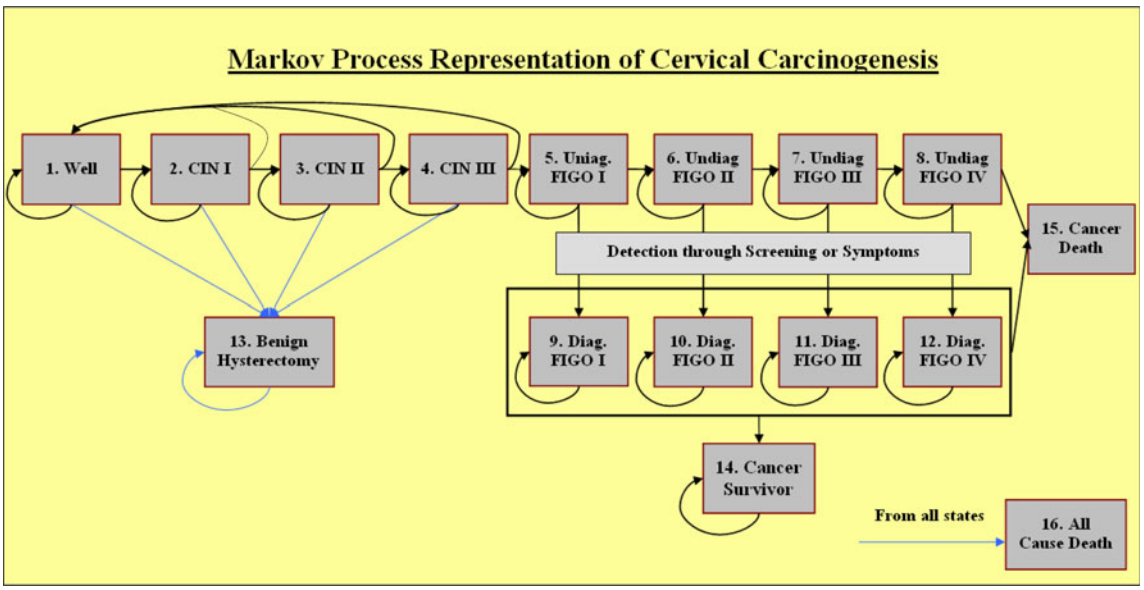

Fig. 1 Graphical representation of the Markov process for the natural history of cervical carcinogenesis

4. CIN III: Severe cell changes on the skin of the cervix (a precancerous state).

From this state, a woman can remain in the same state, regress to well (naturally or upon successful treatment following a true positive test result), progress to FIGO I cervical cancer, move to benign hysterectomy, or die from some cause other than cervical cancer.

5–8. Undiagnosed (Undiag.) FIGO I–IV: Cervical cancer that has not been detected through symptoms or screening.

From these states, a woman can remain on the same stage of cancer, progress to the next stage, develop symptoms and move to diagnosed cancer of the same level, or die from some cause other than cervical cancer. At undetected FIGO IV, the woman can move to death from cervical cancer. Undetected FIGO I–III states do not lead to death from cervical cancer, since it is assumed that symptoms present themselves prior to death. Cancer symptoms are captured by the transitions to the corresponding diagnosed FIGO states.

9–12. Diagnosed (Diag.) FIGO I–IV: Cancer that has been detected through symptoms or screening.

At these states a woman undergoes treatment for cervical cancer according to the stage of the cancer, as described in Section 1.1. If treatment is successful and no reoccurrence of cancer is seen for a period of 5 years, the woman moves to the cancer survivor state. Otherwise, she moves to the cancer death state. During these 5 years a woman can also die from some cause other than cervical cancer.

13. Benign Hysterectomy: Hysterectomy performed for reasons other than cervical cancer.

If hysterectomy is performed for some reason other than cervical cancer, there are no risks for developing precancerous lesions or cervical cancer. Thus, from this state a woman can either stay at the same state or die from some cause other than cervical cancer.

14. Cancer Survivor: Cervical cancer survivor 5 years after cervical cancer diagnosis and treatment.

Women at this state, can remain in the same state, or die from some cause other than cervical cancer. Given survival beyond 5 years, the likelihood of death caused by cervical cancer is rare, which is why this time interval is used [8, 28, 29].

15. Cancer Death: Death due to cervical cancer.
16. All Cause Death: Death due to causes other than cervical cancer.

Tables 1, 2 and 3 summarize the parameters used in the natural history sub-model. The transition probabilities taken from [13] include the annual transition probabilities that describe the natural history of cervical carcinogenesis and the 5-year survival rates for cancer after detection and treatment. Note that in the absence of screening, the transitions from undiagnosed to diagnosed cervical cancer capture the women who develop symptoms and seek treatment. With screening, these transitions capture the women who seek treatment as a result of a positive Pap smear. Hoyert et al. [30] provide data for the transition probabilities into the All Cause Death state, which captures non-cervical cancer deaths. When in the diagnosed FIGO I–IV and undiagnosed FIGO IV states, a woman increases her chance of death by considering cervical cancer deaths. Note that transitions to the Cancer Death and the All Cause Death states are mutually exclusive. The method used to obtain the probabilities from Well to CIN are described in Section 2.2.

In the simulation, when a woman has a Pap smear, she is sent from the natural history sub-model to the screening and treatment sub-model. First, a Pap smear test is performed. If the test is negative, the woman is sent back to the natural history sub-model to the state she was in when she left. If the test result is true positive for CIN I–III, the woman undergoes treatment. Table 2 summarizes the Pap smear sensitivity and specificity rates, which are state-dependent. Pap smears are primarily designed to prevent cervical cancer by detecting CIN I–III. A lower sensitivity level for CIN I reflects the difficulty associated with early detection of CIN I. The Table 2 sensitivity rates assume that a cone biopsy is performed after a positive Pap smear to accurately establish the correct classification of the abnormality. All treatments have a specificity rate of 0.95, which is consistent with the effectiveness levels used in other studies (e.g., [14, 31, 32]). The specificity is only defined with respect to well patients, and hence, it is not defined for women in the CIN I–III or FIGO I–IV states. Likewise, the sensitivity is only defined for women in a diseased state, and hence, it is not defined for women in the Well state. If treatment of CIN I–III is successful, the woman returns to the well state in the natural history sub-model. If treatment is unsuccessful, the woman is returned to the natural history sub-model to the same state she was in when she left. If the test is positive for cancer (undiagnosed FIGO I–IV), then the woman is sent to the corresponding diagnosed FIGO I–V state, where she is treated for cervical cancer.

We set the compliance levels of women at 100%. This means that all women are willing to follow up on screening and treatment. Furthermore, we assume that no surveillance is performed after treatment for abnormal Pap smears. The reasons for these choices are twofold. First, imperfect compliance adds unnecessary complexity to the model that would detract from the goal of this paper. Second, the parameters for compliance and the levels of surveillance vary dramatically depending on the population of interest,

Table 1 Cervical carcinogenesis natural history transition probabilities

Origin state	Destination state	Age	Annual probability
Well	CIN I	15–85	0.0017–0.0521
CIN I	CIN II	15–34	0.0173
		35–85	0.0595
CIN II	CIN III	15–85	0.0567
CIN I	Well	15–34	0.1027
		35–85	0.0645
CIN II	Well	15–34	0.1027
		35–85	0.0645
CIN III	Well	15–85	0.0567
CIN III	Undiag. FIGO I	15–85	0.0410
Undiag. FIGO I	Undiag.FIGO II	15–85	0.2015
Undiag. FIGO II	Undiag. FIGO III	15–85	0.2592
Undiag.FIGO III	Undiag. FIGO IV	15–85	0.3624
Undiag. FIGO I	Diag. FIGO I	15–85	0.1098
Undiag. FIGO II	Diag. FIGO II	15–85	0.2150
Undiag. FIGO III	Diag. FIGO III	15–85	0.6120
Undiag. FIGO IV	Diag. FIGO IV	15–85	0.9000
Diag. FIGO I	Cancer survivor	15–85	0.943
Diag. FIGO II	Cancer survivor	15–85	0.736
Diag. FIGO III	Cancer survivor	15–85	0.594
Diag. FIGO IV	Cancer survivor	15–85	0.238
All	All cause death	15–20	0.000401
		20–24	0.000473
		25–34	0.000640
		35–44	0.001488
		45–54	0.003169
		55–64	0.007380
		65–74	0.018647
		75–85	0.018647
Well, CIN I–III	Benign	15–35	0
	Hysterectomy	35–39	0.0113
		40–44	0.0107
		45–49	0.0107
		50–85	0.0060

unlike the natural history and treatment efficacy parameters. Therefore, considering specific compliance parameters and surveillance levels would remove the general pertinence of the model. However, compliance remains an important issue, since it is one of the most important factors leading to the development of cervical cancer [33]. Compliance can be incorporated into the model by using some of the observations by Whynes et al. [34], who analyze discrepancies between predicted and actual cervical cancer screening attendance and compliance from an economic point of view.

Table 2 Pap smear sensitivity and specificity rates

State	Specificity (%)	Sensitivity (%)
Well	95%	–
CIN I	–	47.1%
CIN II	–	71.8%
CIN III	–	71.8%
Undiag. FIGO I–IV	–	71.8%

2.2 Construction and validation of the model

We built the simulation model using Arena 10.00.00 and performed cross-model validation against the results of Siebert et al. [13] assuming no screening. Siebert et al. [13] did not explicitly define the set of parameters that describe the transition probabilities from Well to CIN I for different ages. They only state that the transition probabilities range

Table 3 Model prediction and cross-model validation values

Model predictions	Siebert et al.	Developed model
Peak age (years) of CIN I	25	25
Peak age (years) of CIN II	38	32–39
Peak age (years) of CIN III	48	43–47
Peak age (years) of cervical cancer incidence	51	40–47
Peak incidence of cervical cancer (per 100,000)	84	76
Cervical cancer incidence (per 100,000)	3,032	3,036
Cervical cancer death (per 100,000)	1,004	799
Percentage of symptoms developed at FIGO I	38.8%	39.0%
Percentage of symptoms developed at FIGO II	31.6%	31.7%
Percentage of symptoms developed at FIGO III	24.1%	23.8%
Percentage of symptoms developed at FIGO IV	5.45%	5.5%

from 0.0017 to 0.0521 for ages 15 to 85, as shown in Table 1. Therefore, we performed calibration on these parameters to match the model output with an observed set of data.

As mentioned in Section 2.1, one advantage of the Siebert et al. [13] model is that it provides many predictions in the absence of screening, which allows a detailed calibration. The age-specific prevalence of CIN I was used to calibrate the Well to CIN I transition probabilities. We then determined the Well to CIN I transition probabilities that minimize the deviation of the age-specific prevalence rates provided by [13]. The optimization model used is

$$\min \sum_{i=15}^{85} \left| CINI_i - CIN_i^{OBS} \right|$$

Subject to:

$$0.0017 \leq P(WellToCINI_i) \leq 0.0521,\ i = 15,\ \ldots,\ 85$$

where $CINI_i$ is the CIN I prevalence at age i from the Siebert et al. [13] model, $CINI_i^{OBS}$ is the CIN I prevalence at age i observed in the developed model, and $P(WellToCINI_i)$ is the transition probabilities from Well to CIN I.

Table 3 summarizes the age-specific prevalence rates of CIN I–III and total CIN as predicted by the developed model, along with the CIN I prevalence as predicted by the Siebert et al. [13] model. Figure 2 depicts the CIN II, CIN III, and CIN Total (= CIN I + CIN II + CIN III) prevalence rates from the developed model. Figure 2 also shows the match between the CIN I prevalence rates from our model and the Siebert et al. [13] model.

Table 3 summarizes the cross-model validation values that compare several measurements in the developed model to the Siebert et al. [13] model. For the peak ages of CIN II and CIN III, Table 3 gives ranges of ages instead of one age. This is because those ages exhibited the same prevalence rates to three decimal points. The peak age for cervical cancer incidence also has a range, because those ages have the same cancer incidence within one cancer per 100,000. The discrepancy in cervical cancer deaths is because our model incorporates women dying from other causes during the 5 years after cancer detection and treatment, whereas Seibert et al. [13] do not. The "percentage of symptoms developed" values report the conditional proportion of symptoms that develop at each cancer stage in the absence of screening.

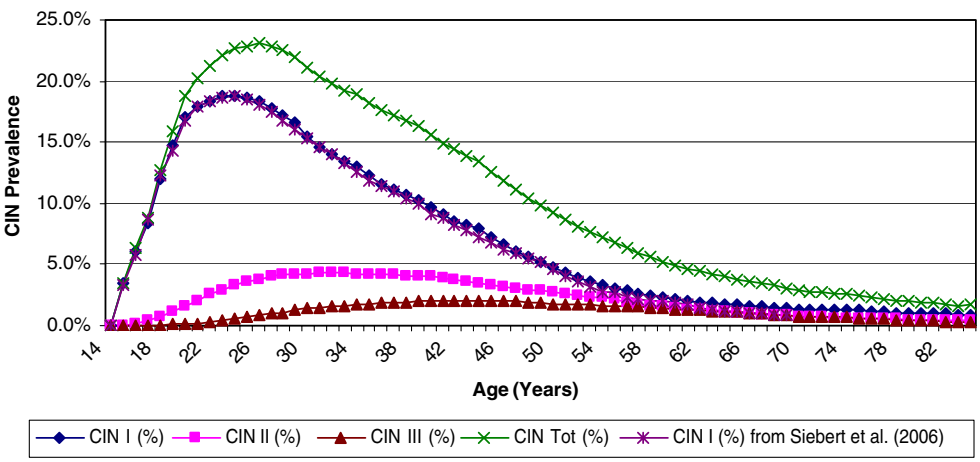

Fig. 2 Age-specific CIN prevalence from simulated model

2.3 Simulation-optimization model

The objective function for the simulation-optimization captures the expected health benefits that result from the screening strategies. Three performance measures (f_1, f_2, and f_3) are used for the objective function value:

1. the expected reduction in cancer incidences (f_1),
2. the expected reduction of cancer deaths (f_2), and
3. the expected life years saved in the screened population (f_3).

These objectives are not conflicting objectives in the sense of multi-objective optimization. They are alternative objectives that decision makers might use in different healthcare scenarios. In fact, minimizing cancer incidence is a means to minimizing cancer deaths. Minimizing cancer deaths is in turn a means to maximizing life years saved. Thus, each might be considered fundamental to different healthcare decision contexts, in the language of value-focused thinking [35]. For this reason, we study all three in separate optimizations.

The control variables are $\boldsymbol{X} = (X_1, X_2,...,X_n)$, where X_i = denotes the age the i^{th} screening to be performed, $i = 1... n$, $X_i \in Z^+$ and n is the number of lifetime screenings available. We could have used a binary integer model, but this formulation would not have been as practical for discrete event simulation. To compute the number of life years lost, we compared the difference in the simulated remaining lifetime (in years) in a women with cervical cancer who is screened and found to have cervical cancer to the same woman who is never screened.

There are two sets of constraints in the model. The first set of constraints ensures that each screening age is between 15 and 85. The second set of constraints requires that the first screening occurs before the second and so on. This second set of constraints is not essential for the simulation-optimization model to work properly, but it does help to reduce the number of solutions considered. The formulation of the optimization models is then as follows:

$$\begin{gathered} \operatorname{Min} f_j(\boldsymbol{X}) \\ \text{Subject to}: \ 15 \leq X_i \leq 85, \ i = 1, \ldots, n \\ X_i + 1 \leq X_{i+1}, \ i = 1, \ldots, n-1 \\ X_i \in Z^+ \end{gathered}$$

where X_i = the age the i^{th} screening is to be performed, n = the number of available lifetime screenings, $\boldsymbol{X} = (X_{1,\ \ldots,}\ X_n)$, and $f_j(\boldsymbol{X})$ is the jth objective considered, j = 1,2,3.

3 Analysis and results

This section reports the results from the simulation-optimizations and illustrates how the heuristic optimum solutions can provide policy recommendations for practical screening strategies. Heuristic optimum solutions refer to the near-optimal solutions identified by the simulation-optimization procedure [36]. Finally, we perform an analysis on those strategies, comparing them to constant interval screening strategies, which have been used in practice and considered in the literature.

Arena 10.00.00 was used to create the simulation model, and OptQuest from OptTek Systems Inc. was used to perform simulation-optimization, which integrates meta-heuristics such as Tabu search, neural networks, and scatter search, into a single composite method. The expected value at each candidate solution was estimated with three replications. We set OptQuest to check a minimum of 1,400 solutions. We ran 30 replications of the top 25 solutions to get expected values that are more accurate. Then, we consider the solution with the best expected value to be the heuristic optimum screening strategy. On an Intel ® Pentium ® D CPU 3.40 GHz, 2.00 GB of RAM system, the optimization required approximately 35 h for the first 1,400 solutions (for a single number of lifetime screenings) and approximately two and a half days to perform the entire optimization process. We tested 3, 4 and 5 replications per solution in Optquest. We observed that the best solution did not change for the cancer incidence and cancer deaths objectives, but the life years lost objective required 4 or 5 replications per solution to obtain a stable outcome due to its higher variance. Thus, we selected the minimum number of replications given the long run-times. The starting solutions were also varied across extremes of the possible solutions, but the best solution found did not change. Variance reduction techniques were not used, although techniques like common random numbers could be implemented in practice.

For each of the three objective functions (cancer incidence, cancer death, and life years lost), one to 22 lifetime screenings were considered. Sixty-six distinct optimizations were performed, each of which corresponds to a fixed number of available lifetime screenings (from 1 to 22) and for one of the three objective function values. We did not consider more than 22 lifetime screenings, because the improvement in the objective function values for more screenings was almost zero for all three measures. Furthermore, the constant interval screening strategy of screening every 3 years from 20 to 85 years of age requires 22 screenings.

Tables 4, 5, and 6 summarize the heuristic optimum solutions with respect to cancer incidence, cancer deaths, and life years lost, along with their objective function values estimated from 30 replications at each solution. For example, if there is one lifetime screening, then it is performed at age 35 for the cancer incidence and cancer deaths measures and at 33 for the life years lost measure. If

Table 4 Heuristic optimum solutions with respect to cancer incidence (f_1)

Life screenings available	Expected cancer incidence per 100,000, n=30	95% half width	Heuristic optimal solution with respect to cancer incidence																						
0	3,034	21																							
1	1,846	15	35																						
2	1,260	12	30	43																					
3	878	11	28	37	47																				
4	662	11	26	31	38	49																			
5	514	9	24	30	36	40	52																		
6	405	7	24	29	33	39	47	52																	
7	330	7	22	26	33	36	39	50	54																
8	269	6	23	28	31	34	41	45	51	55															
9	210	6	23	26	29	32	36	40	44	50	58														
10	177	5	22	26	28	32	35	39	44	48	53	62													
11	161	4	24	25	26	29	33	36	39	41	46	53	62												
12	131	4	22	24	28	30	33	36	40	43	48	51	57	61											
13	109	4	22	25	26	29	32	36	38	40	42	45	51	58	65										
14	99	3	21	22	24	27	28	33	35	38	42	44	47	50	60	66									
15	85	3	22	25	26	30	31	33	35	37	39	42	44	48	52	54	62								
16	73	3	20	23	24	25	29	31	33	36	39	41	43	48	50	53	61	67							
17	64	3	19	20	23	25	27	30	32	33	37	39	41	44	45	50	52	59	69						
18	54	3	20	21	23	25	28	30	31	33	36	37	39	42	45	46	50	58	66	73					
19	50	3	20	22	25	27	29	31	32	36	37	39	40	45	46	47	48	55	56	62	71				
20	42	3	20	21	23	24	27	29	30	33	36	37	39	43	44	48	52	54	59	60	66	72			
21	38	2	19	21	23	25	26	28	30	32	34	36	37	38	41	43	48	49	53	55	60	63	70		
22	34	2	20	21	24	25	27	31	32	33	35	36	40	41	44	46	48	48	54	57	58	60	65	72	

Table 5 Heuristic optimum solutions with respect to cancer deaths (f_2)

Life screenings available	Expected cancer deaths per 100,000, n=30	95% half-width	Heuristic optimal solution with respect to cancer deaths																						
0	827	10																							
1	454	9	35																						
2	277	7	31	42																					
3	184	5	30	39	46																				
4	129	4	28	32	41	50																			
5	91	4	27	30	37	43	53																		
6	69	4	24	29	34	41	45	54																	
7	52	4	24	28	32	36	45	50	53																
8	44	2.5	26	30	31	34	42	49	51	58															
9	33	2.5	23	27	28	34	38	42	46	52	63														
10	27	1.5	22	26	30	33	35	41	42	48	54	65													
11	22	1.5	24	26	27	29	34	35	42	44	50	54	68												
12	17	1.5	23	25	29	30	34	38	39	41	48	51	58	61											
13	14	1	22	25	27	30	35	37	40	41	46	49	50	71	71										
14	12.5	1	20	23	26	29	32	34	37	38	41	43	48	61	61	68									
15	11.5	1	24	25	28	31	33	36	38	39	40	46	48	55	55	57	68								
16	9.3	1	22	24	27	31	32	35	37	40	41	44	51	54	54	56	58	68							
17	8.1	1	20	21	26	28	29	31	33	35	37	41	46	48	48	52	54	64	71						
18	6.2	1	22	23	24	27	31	32	35	38	39	41	42	48	48	49	51	60	62	72					
19	5.9	1	20	23	25	27	28	30	31	33	37	39	41	48	48	51	53	60	62	67	69				
20	5.3	1	20	22	25	26	29	30	31	35	38	39	40	45	45	48	50	53	54	57	65	68			
21	5.2	1	22	23	24	29	30	31	33	35	40	42	44	49	49	53	54	55	56	62	63	68	74		
22	5.1	1	19	22	24	25	28	29	32	34	37	38	39	44	44	48	49	50	51	53	56	58	59	52	

Table 6 Heuristic optimum solutions with respect to life years lost (f_3)

Life screenings available	Expected life years lost per 100,000, n=30	95% half-width	Heuristic optimal solution with respect to life years lost																						
0	21,380	284																							
1	11,487	220	33																						
2	7,003	200	29	36																					
3	4,704	181	27	31	41																				
4	3,215	135	25	30	37	46																			
5	2,293	110	24	29	32	40	49																		
6	1,725	95	25	27	32	37	43	49																	
7	1,272	79	23	26	31	33	38	44	51																
8	1,007	85	22	27	28	31	35	40	46	49															
9	760	79	23	26	28	32	36	39	44	51	52														
10	654	54	21	23	25	29	30	34	394	42	26	49													
11	533	46	21	23	25	29	32	34	40	42	50	52	57												
12	453	48	21	23	24	28	29	31	36	37	46	47	48	60											
13	319	35	21	23	25	27	30	32	35	37	42	43	45	52	57										
14	280	32	22	23	24	27	29	32	35	36	37	41	44	47	52	59									
15	231	28	20	23	24	27	28	29	33	35	36	40	44	46	49	53	61								
16	181	28	22	22	24	25	28	30	32	34	35	41	43	44	47	48	54	60							
17	168	31	20	22	24	26	28	31	32	35	37	40	42	45	46	50	54	55	57						
18	129	30	18	21	23	26	27	30	31	33	35	26	38	41	42	43	44	53	55	61					
19	123	30	19	22	24	26	27	28	29	31	35	36	37	38	40	41	45	49	54	56	65				
20	115	25	20	21	22	24	25	27	30	31	33	35	37	38	43	44	45	49	50	51	60	63			
21	111	24	20	21	23	24	25	26	27	30	31	36	37	38	40	41	44	45	49	50	52	56	57		
22	104	24	21	21	23	26	29	30	32	33	34	35	38	40	44	46	47	48	50	52	56	57	58	61	

there are two lifetime screenings, then they are performed at ages 30 and 43 for the cancer incidence measure, 31 and 42 for the cancer deaths measure, and 29 and 36 for the life years lost measure. Figure 3 illustrates the benefits resulting from implementing the optimal screening strategy for each of the three objectives as a function of the number of lifetime screenings. In Fig. 3, the proportion of benefits received is computed as the difference in the benefits when compared to the base case without screening (either expected cancer incidence, expected cancer deaths, or expected life years lost), normalized by the benefits received in the base case without screening. For a given number of lifetime screenings, Fig. 3 shows that the relative benefits of the cancer incidence measure is less than that of the cancer deaths and life years lost measures. As more screenings are performed, cervical cancer is detected earlier, which disproportionally prevents cancer deaths—and life years lost as a result of cancer death—as compared to cancer incidence.

The objective function values reflect the mean performance. Given a specified number of replications, a confidence interval can be obtained for the mean value for any specified screening strategy. The size of the confidence interval depends on the number of replications performed and the variability of the objective function value across the replications. A minor change in the screening strategy, such as moving a single screening by 1 year, would result in a small change in the objective function value, which maybe insignificant when comparing the associated confidence intervals. Thus, the confidence intervals of the heuristic optimum solutions and the confidence intervals of a few similar screening strategies overlap. We refer to the set of possible screening strategies whose confidence intervals overlap with that of the heuristic optimum solution as the *optimality region*. Note that the optimality region is a function of the number of replications performed, since this determines the width of the confidence intervals. Increasing the number of replications narrows the confidence intervals, which makes the optimality region smaller. We performed 30 replications per scenario in order to identify dynamic screening policies. To increase the likelihood of finding the global optimal solution, additional replications could be performed. Even better, ranking and selection methods could be applied to allocate additional replications optimally to solutions in the optimality region until we can confidently identify the best solutions (see [37] for a review and performance comparison of several ranking and selection methods). The estimated objective values of the heuristic optimum solutions are important in the sense that they provide a heuristic lower bound of what can be achieved with a specific number of lifetime screenings. Therefore, we can use the heuristic optimum solutions to construct practical screening policies.

The number of feasible solutions in the optimality region depends on the total number of lifetime screenings available as well as the total number of replications. The fewer the number of screenings, the fewer the number of solutions in the optimality region. It was possible to enumerate all such solutions in the optimality region for only a small number of lifetime screenings (e.g., four or fewer). Considering all combinations of screening ages when more lifetime screenings are available resulted in a large increase in the number of solutions in the optimality region. For example, lengthening the time between screenings by 1 year could shift all of the screenings by 1 year (e.g., screening every 5 years starting at age 46 vs. 45), which would represent a new solution while having a negligible effect on the objectives. However, the nature of

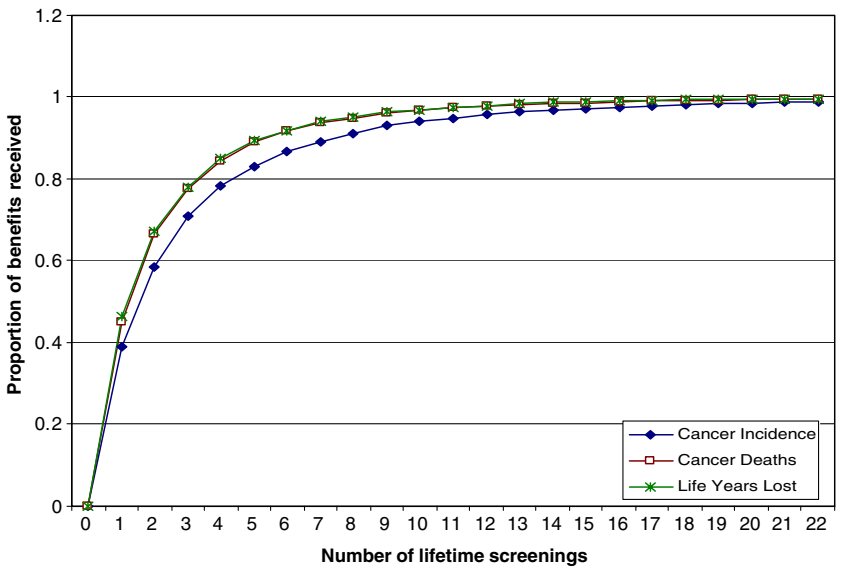

Fig. 3 The proportion of benefits received for each objective as a function of the number of lifetime screenings

the optimality region is the same across all three objectives—the solutions are similar in that the overall spacing between screenings are the same between slightly different age ranges (e.g., screen every 2 years from 35 to 45 versus screen every 2 years from 36 to 46).

The sensitivity of the results with respect to its parameters is an important consideration. Sensitivity has been extensively discussed in the medical literature. For brevity, we summarize our observations as well as those in the literature. It has been reported that the screening times are sensitive to the test sensitivities and the CIN regression rates [8, 11, 12, 14]. The benefits of a screening strategy can be sensitive to parameters while the underlying screening times remain the same. It has been reported that the benefits are sensitive to the costs, test sensitivities, the rate of HPV incidence, and the CIN progression rates [8, 13, 14, 38].

3.1 Constructing practical screening strategies from the heuristic optimum solutions

The heuristic optimum solutions from Tables 4, 5, and 6 have one shortcoming compared to existing constant interval screening strategies used in practice. They lack a visible pattern. Hence, they are not as practical to prescribe. Strategies that have a more visible pattern, while maintaining their effectiveness, would be more suitable to use as policy recommendations. They would be simpler to understand and more likely to be followed by the screened population. Therefore, we searched the optimality region for solutions with smooth patterns that were equally effective but easier to follow. The goal is to provide solutions with constant screening intervals as much as possible across different age ranges while targeting screening ages that are multiples of 5 or 10, since patterns are more easily recognizable with such numbers. For example, a smoothed screening strategy with 12 lifetime screenings available could have a screening interval of 3 years from 22 to 46 years of age and a screening interval of 5 years from 50 to 60 years of age (instead of screening every 5 years from 51 to 61). Such policies would be useful from the patient and provider perspective, since they result in patients returning every 3 years (or 5 years) for a long time interval. The smoothed screening policies would also be useful to post in a clinic or on a web page, since the screening ages do not depend on the patients' screening histories (which would result in different screening ages for different patients). In addition, doctors and insurance companies could use standard procedures to remind patients to schedule an appointment when screenings are scheduled several years apart (e.g., by mailing a card to patients). Note that this does not preclude developing separate schedules or stopping policies for specific subpopulations based on risk and other factors.

We constructed the smoothed screening strategies using the following procedure. We considered the objective value of a candidate solution to be not significantly different from the heuristic optimum if their 95% confidence intervals overlap (given 30 replications). More specifically, the goal is to minimize one of the three objectives (expected cancer incidence, cancer death, and life years lost). Thus, a candidate smoothed-solution has to have an objective function value no larger than the value of the heuristic optimum screening strategy plus the value of its 95% half-width. We used 30 replications because the sizes of the resulting half-widths were sufficiently small for all three performance-measures from a practical point of view. Tables 4, 5, and 6 show the sizes of the half-widths at various levels of cancer incidence, cancer deaths, and life years respectively. We observed that solutions for cancer incidence and cancer death deviating more than two (sometimes three) years from the ages of the heuristic optimum solutions rarely maintained objective function values within the 95% confidence interval of the heuristic optimum. Note that this search procedure could be included in the simulation-optimization process in order to find the "optimized" strategies by including the three objectives in the model (such as by considering a weighted combination of the three objectives or by optimizing the three objectives in a lexicographical order) and by including additional constraints to enforce screening at equally spaced intervals. This would be challenging to implement, since the regions with equally spaced screenings can vary within the model. Alternatively, a heuristic could be used to search for alternative screening strategies by considering a relatively small number of screening strategies.

There is a great deal of overlap among the optimality regions of the three objectives, even though the optimality regions are not large, meaning that screenings tend to be scheduled at the same ages across different performance measures. This is of interest, since it suggests that different performance measures would not necessarily lead to different screening policies in practice. For example, the heuristic optimum solutions of cancer incidence and cancer death in Tables 4 and 5 are almost identical. In fact, the majority of the screening ages are 2 years or less apart. The cancer death screening ages are mostly 1 year later than the screening ages for cancer incidence. This indicates that optimality regions of cancer incidence and cancer deaths overlap. The heuristic optimum solutions for life years saved in Table 6 are slightly smaller than the screening ages for cancer incidence and cancer deaths (in Tables 4 and 5). They occur on average 2 to 3 years before the screening ages for cancer incidence. As a result, we can construct one set of smoothed screening strategies that are not significantly different to the heuristic optimal solutions for all three objectives. In most cases, any increase in the objective

values are within the 95% confidence interval. The only exceptions are four screening strategies (4, 6, 15, and 18 lifetime screenings available). For these screening strategies, the life years lost marginally deviates from the 95% confidence intervals of the heuristic optimum values.

Table 7 provides the smoothed dynamic screening strategies that are also practical to prescribe as screening policy strategies. These are compared to the constant interval screening strategies of 2, 3, and 5 years considered in the literature and used in practice. Table 8 summarizes the objective values with respect to all three objective functions. It is worth noting that since the half-widths from 30 replications are small, the heuristic optimal solutions and the smoothed strategies are effectively identical. The smoothed strategies are more intuitive and have a visible pattern that makes them easily understood. For example, we can easily express the dynamic screening strategy for 12 available lifetime screenings as follows: "The screening strategy with 12 available lifetime screenings is screening every 3 years from 22 to 46 years of age and (after 4 years) screening every 5 years from 50 to 60 years of age". Note that screening every 5 years from 46 to 61 is less desirable from a policy perspective, since it would result in screening ages that are not multiples of five or ten (screening at 51, 56, and 61 instead of at 50, 55, and 60). Furthermore, the dynamic screening strategies are intuitive, since the screening intervals that they recommend are smaller at ages where the risks of CIN and cervical cancer are higher and larger at ages where the risks are lower.

3.2 Discussion

The screening strategies obtained by smoothing the heuristic optimum solutions are cost-effective, particularly when the number of screenings is small. For example, screening women only once in their lifetime at the age of 35 reduces cancer incidence by 39%, which is consistent with the results reported by Goldie et al. [11]. One screening at 35 also reduces cancer deaths and life years lost by approximately 45%. The screening strategy with three lifetime screenings reduces cancer incidence, cancer death, and life years lost by more than 70%. The screening strategy with seven lifetime screenings reduces cancer incidence, cancer death and life years lost by approximately 90%.

At higher numbers of lifetime screenings, we can also see the effectiveness of the constructed screening strategies by comparing them to constant interval screening strategies, reported in Table 7, and their corresponding objective values with respect to all three objective functions used in the optimizations, summarized in Table 8. In fact, we can compare a constant interval screening strategy to two dynamic screening strategies: (1) the dynamic strategy that provides approximately the same health benefits and (2) the dynamic strategy that uses the same lifetime screenings as the constant interval screening strategy.

The first constant interval screening strategy we will use for comparison is screening every 5 years from ages 20 to 85, which requires 14 lifetime screenings. The dynamic screening strategies that we compare to this constant interval screening strategy have the smallest number of screenings such that its performance measure lies within the 95% confidence interval or is better than the constant interval screening strategy. By looking at Table 8, we can see that the dynamic screening strategy with ten lifetime screenings performs comparably with respect to cancer incidence and with respect to cancer deaths. The dynamic screening strategy with eight lifetime screenings performs comparably with respect to life years lost. As a result, the dynamic screening strategies provide approximately the same health benefits as the constant interval screening strategy with four to six fewer scheduled screenings. The dynamic screening strategy with fourteen lifetime screenings performs substantially better than the constant interval screening strategy: it results with 100 cancer incidences, 12 cancer deaths, and 315 life years lost per 100,000 (compared to 201 cancer incidences, 30 cancer deaths, and 1,082 life years lost per 100,000 with the constant interval screening strategy).

The second constant interval screening strategy that we use for comparison is screening every 3 years from 20 to 85 years of age, which requires 22 scheduled lifetime screenings. By looking at Table 8, we can see that the dynamic screening strategy with 16 lifetime screenings performs comparably with respect to cancer incidence (72 per 100,000 for both) and with respect to cancer deaths (9 cancer deaths per 100,000 for both). The dynamic screening strategy with 13 lifetime screenings performs comparably with respect to life years lost (353 versus 354 life years lost per 100,000). As a result, the dynamic screening strategies provide approximately the same health benefits as the constant interval screening strategy with six to nine fewer scheduled screenings. The dynamic screening strategy with 22 lifetime screenings performs substantially better than the constant interval screening strategy: it results with 38 cancer incidences, 4.2 cancer deaths, and 95 life years lost per 100,000 (compared to 72 cancer incidences, 9 cancer deaths, and 354 life years lost per 100,000 with the constant interval screening strategy). It is also worth noting that the dynamic screening strategy with 22 lifetime screenings results to the same life years lost (with 95 life years lost per 100,000) as the constant interval screening strategy of screening every 2 years which requires 33 scheduled lifetime screenings. As a result, the screening strategies constructed through the heuristic optimum solutions dominate the constant interval screening strategies with respect

Table 7 Dynamic screening strategies constructed by smoothing the heuristic optimum solutions, and constant interval screening strategies

Lifetime screenings available	Screening strategies																						
0	–																						
1	35																						
2	30	42																					
3	28	35	45																				
4	28	32	40	48																			
5	24	30	36	42	50																		
6	25	30	35	40	45	50																	
7	24	28	32	36	40	46	52																
8	22	25	30	35	40	45	50	55															
9	22	25	28	32	35	40	45	50	60														
10	22	25	28	32	36	40	44	48	52	60													
11	22	25	28	31	34	37	40	43	46	50	60												
12	22	25	28	31	34	37	40	43	46	50	55	60											
13	22	24	26	29	32	35	38	41	44	47	50	55	65										
14	22	24	26	28	30	32	35	38	41	44	47	50	55	65									
15	22	24	26	28	30	32	35	38	41	44	47	50	55	60	65								
16	20	22	24	26	28	30	32	35	38	41	44	47	50	55	60	65							
17	20	22	24	26	28	30	32	34	36	38	40	42	45	50	55	60	70						
18	20	22	24	26	28	30	32	34	36	38	40	42	45	50	55	60	65	70					
19	20	22	24	26	28	30	32	34	36	38	40	42	44	46	50	55	60	65	70				
20	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	55	60	65	70			
21	19	21	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	60	65	70		
22	19	21	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	60	65	70	
Every 5 years (14)	20	25	30	35	40	45	50	55	60	65	70	75	80	85									
Every 3 years (22)	20	23	26	29	32	35	38	41	44	47	50	53	56	59	62	65	68	71	74	77	80	83	
Every 2 years (33)	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60	...	84

Table 8 Objective values output of the screening strategies evaluated from 30 simulation replications with cohorts of 100,000 women

Lifetime screenings	Cancer incidence per 100,000	95% half width	Cancer incidence prevented (%)	Cancer deaths per 100,000	95% Half width	Cancer deaths prevented (%)	Life years lost	95% half widt	Life years lost
0	3,034	21	0.0%	827	10	0.0%	21,380	284	0.0%
1	1,846	15	39.2%	454	9	45.1%	11,532	305	46.1%
2	1,260	12	58.5%	282	7	65.9%	7,189	240	66.4%
3	874	11	71.2%	189	5	77.1%	4,790	120	77.6%
4	673	9	77.8%	132	4	84.0%	3,428	135	84.0%
5	510	9	83.2%	96	4	88.4%	2,411	115	88.7%
6	410	7	86.5%	71	4	91.4%	1,891	95	91.2%
7	322	7	89.4%	56	3	93.2%	1,314	79	93.9%
8	269	6	91.1%	43	2.5	94.8%	1,125	85	94.7%
9	209	6	93.1%	34	2.5	95.9%	805	81	96.2%
10	181	5	94.0%	26	1.5	96.9%	703	55	96.7%
11	160	4	94.7%	23	1.5	97.2%	558	46	97.4%
12	133	4	95.6%	18	1.5	97.8%	485	48	97.7%
13	113	4	96.3%	14	1	98.3%	353	36	98.3%
14	100	3	96.7%	12	1	98.5%	315	47	98.5%
15	88	3	97.1%	11	1	98.7%	283	29	98.7%
16	72	3.5	97.6%	9	1	98.9%	223	28	99.0%
17	64	3.5	97.9%	8	1	99.0%	172	31	99.2%
18	57	3	98.1%	7	1	99.2%	176	30	99.2%
19	48	3	98.4%	5	1	99.4%	130	19	99.4%
20	45	3	98.5%	4.8	1	99.4%	131	26	99.4%
21	40	2	98.7%	4.5	1	99.5%	133	36	99.4%
22	38	2.5	98.7%	4.2	1	99.5%	95	22	99.6%
Every 5 yrs (14)	201	5	93.4%	30	2	96.4%	1,082	71	94.9%
Every 3 yrs (22)	72	3	97.6%	9	1	98.9%	354	46	98.3%
Every 2 yrs (33)	26	2	99.1%	2.3	0.5	99.7%	98	27	99.5%

to the three performance measures when considering the number of scheduled screenings.

Although we evaluate the screening strategies with respect to cancer incidences, cancer deaths, and life years lost, we report other relevant outputs in Table 9. "Screenings performed" refers to the actual number of screening performed per 100,000 women for each screening strategy (as opposed scheduled screenings). "False positives" refers to the number of false positives. "False positives percentages" refers to the percentage of the actual screenings performed that results in false positive for each screening strategy. "Cancers Detected by Screening" refers to the average number of cancers detected by a Pap smear before symptoms developed. "Cancers Detected by Screening (%)" refers to the conditional proportion of cancer detected by a Pap smear before symptoms developed. "FIGO I–IV Treated" refer to how many women per 100,000 received treatment for cervical cancer at each FIGO state based on either screening or symptoms, which is why some women are treated for cancer in the absence of screening. "FIGO Treated Prevented (%)" refers to the proportion of all FIGO treatments prevented compared to the total number of FIGO treatments in the absence of screening.

Table 9 shows that as the number of screenings increases, the conditional proportion of cancers detected by screening also increases. The absolute number of cancers detected by screening decreases, since cancer incidence is reduced as the number of lifetime screenings increases. This demonstrates the benefits of screening not only in detecting abnormal smears and preventing cancer, but also in detecting asymptomatic cancer. This allows treatment at earlier stages of the cancer than otherwise possible. Figure 3 and Table 8 also report this health benefit of screening, where the proportion of cancer deaths prevented is higher than the percentages of cancer incidences prevented as the number of screening increases.

Table 9 shows that the conditional proportion of cancers detected by screening (as opposed to detection through symptoms) is lower for the dynamic screening strategies when compared to the constant screening strategy with the

Table 9 Additional output from the simulation

Lifetime screenings	Screenings performed	False positives	False positive percentage	Cancers detected by screening	Cancers detected by screening (%)	FIGO I treated	FIGO II treated	FIGO III treated	FIGO IV treated	FIGO prevented (%)
0	0	0	0.00%	0.0	0.0%	1035.7	840.6	628.8	348.2	0.0%
1	98,714	3,985	4.04%	201.3	10.9%	716.7	490.1	332.7	179.2	39.8%
2	186,889	7,686	4.11%	246.1	19.5%	539.1	321.4	206.0	103.7	59.0%
3	286,051	11,988	4.19%	199.5	22.8%	392.4	224.0	132.9	67.9	71.4%
4	374,533	15,907	4.25%	187.7	27.9%	316.3	165.6	92.2	45.0	78.3%
5	473,402	20,620	4.33%	150.8	29.6%	241.6	117.8	67.4	33.0	83.9%
6	561,477	24,677	4.40%	147.2	35.9%	206.2	88.7	47.4	43.0	86.5%
7	651,538	28,617	4.39%	125.5	39.3%	170.5	75.8	36.3	16.7	89.5%
8	739,733	32,904	4.45%	110.1	40.9%	139.0	58.6	26.7	12.7	91.7%
9	833,970	37,330	4.48%	91.0	43.5%	114.7	43.8	20.5	9.3	93.4%
10	917,055	41,447	4.52%	88.8	49.0%	105.3	37.9	14.0	3.8	94.3%
11	1,021,053	46,504	4.55%	77.1	48.2%	92.9	35.2	14.4	6.4	94.8%
12	1,098,761	50,308	4.58%	65.2	49.0%	77.6	26.0	10.3	3.3	95.9%
13	1,188,834	54,475	4.58%	55.7	49.3%	63.8	20.5	8.3	3.6	96.6%
14	1,283,148	59,004	4.60%	49.2	49.2%	56.4	17.3	7.0	3.2	97.1%
15	1,361,810	62,858	4.62%	47.2	53.7%	52.1	14.3	5.4	2.4	97.4%
16	1,461,662	67,521	4.62%	34.3	47.6%	40.9	12.6	4.5	2.1	97.9%
17	1,557,517	72,145	4.63%	31.8	49.7%	37.2	10.5	4.6	2.3	98.1%
18	1,626,192	75,536	4.66%	32.9	57.8%	36.6	8.7	3.1	1.2	98.3%
19	1,714,357	80,040	4.67%	27.7	57.8%	30.6	7.9	2.7	0.8	98.5%
20	1,799,106	84,183	4.68%	25.8	57.3%	28.5	6.8	1.9	0.8	98.7%
21	1,891,147	88,593	4.68%	21.9	54.8%	24.5	5.7	1.9	0.7	98.8%
22	1,969,550	92,481	4.70%	21.7	57.0%	23.0	5.6	1.6	0.7	98.9%
Every 5 years (14)	1,068,266	49,142	4.60%	127.0	63.2%	130.1	45.1	16.3	5.3	93.1%
Every 3 years (22)	1,714,695	80,575	4.70%	55.1	76.5%	54.1	12.7	12.9	1.1	97.5%
Every 2 years (33)	1,969,550	92,481	4.70%	21.3	82.1%	20.3	3.3	0.7	0.1	99.1%

same number of lifetime screenings. This proportion is lower because constant interval screening occurs with the same frequency at early ages (when cancer is preventable) as in later ages (when cancer is more likely to have been developed). As a result, the constant interval screening strategies detect fewer cancers at early ages and are more likely to detect them at later ages. This indicates that although the dynamic screening strategies prevent more cervical cancers from forming, cancer tends to be identified when it is in more advanced stages. A second advantage of the constant interval screening strategies is that they result in fewer total number of screenings performed when compared to the dynamic screening strategies with the same number of scheduled lifetime screenings. The equally spaced screenings in the constant interval screening strategies schedule many screenings later in life when women cannot use them (due to hysterectomy, cancer, or death), and hence, these screenings never take place.

False positives are an important issue when it comes to any type of screening in medicine. This is true for cervical cancer screening as well. A Pap smear costs about $35 US [11]. If the smear result is positive, it is followed by a colposcopy and biopsy that cost approximately $450–1,281 US [11, 39]. Although false positives comprise a small percentage of the overall number of screenings performed, they result in substantially large costs [27, 39]. Table 9 shows that there is a small increase in the proportion of screenings that result in a false positive as the number of lifetime screenings increases. This is due to a decrease in the number of women without abnormal lesions as the number of scheduled lifetime screenings increases, and hence, the conditional proportion of screenings that result in false positives increases.

Heuristic optimum solutions obtained by simulation-optimization are equally effective as traditional methods and their smoothed solutions can serve as practical

Table 10 Heuristic optimum solutions that minimize cancer incidence with 1, 2, 3, 5, and 8 lifetime screening as the duration of sustained vaccine immunity increases

Vaccine sustained immunity (Age)	Screenings available	Heuristic optimal solution	Cancer incidence per 100,000	95% half width	Cancer incidence prevented (%)	Cancer deaths per 100,000	95% half width	Cancer deaths prevented (%)	Life years lost per 100,000	95% half width	Life years lost prevented (%)
No vaccine (smoothed solutions)	0	–	3,034	21	0.0%	827	10	0.0%	21,380	284	0.0%
	1	35	1,846	15	39.2%	454	9	45.1%	11,532	220	46.1%
	2	30, 42	1,260	12	58.5%	282	7	65.9%	7,189	240	66.4%
	3	28, 35, 45	874	11	71.2%	189	5	77.1%	4,790	120	77.6%
	5	24, 30, 36, 40, 52	510	9	83.2%	96	4	88.4%	2,411	115	88.4%
	8	22, 25, 30, 35, 40, 45, 50, 55	269	6	91.1%	43	2.5	94.8%	1,125	85	94.8%
20	0	–	2,440	21.5	0.0%	656	10	0.0%	15,653	250	0.0%
	1	39	1,462	12	40.1%	351	7	46.5%	8,622	211	44.9%
	2	34, 45	961	10	60.6%	218	5	66.8%	5,458	168	65.1%
	3	29, 38, 47	686	9	71.9%	145	4.5	77.9%	3,433	120	78.1%
	5	28, 32, 37, 44, 51	388	7	84.1%	72	3	89.0%	1,655	84	89.4%
	8	27, 29, 33, 39, 42, 47, 53, 60	201	6	91.8%	31	2	95.3%	813	68	94.8%
25	0	–	2,006	16	0.0%	534	7	0.0%	12,027	189	0.0%
	1	42	1,198	13	40.3%	287	6	46.3%	6,690	162	42.7%
	2	35, 46	789	9	60.7%	179	4.5	66.5%	4,264	131	64.5%
	3	35, 40, 49	495	8	75.3%	114	3.5	78.7%	2,856	120	76.3%
	5	29, 35, 41, 49, 55	331	6	83.5%	61	3	88.6%	1,573	82	86.9%
	8	24, 30, 35, 37, 44, 46, 51, 59	177	6	91.2%	27	2	94.9%	665	56	94.5%
30	0	–	1,656	15	0.0%	437	6	0.0%	9,569	166	0.0%
	1	44	1,008	9	39.1%	241	5	44.9%	5,861	160	38.8%
	2	39, 49	682	9	58.8%	149	4.5	65.9%	3,814	136	60.1%
	3	34, 44, 50	465	8	71.9%	102	4	76.7%	2,610	92	72.7%
	5	29, 36, 43, 49, 57	288	5	82.6%	54	3	87.6%	1,407	87	85.3%
	8	26, 30, 34, 39, 45, 49, 51, 65	156	5	90.6%	25	2	94.3%	640	46	93.3%
35	0	–	1,387	15.5	0.0%	365	6	0.0%	7,976	152	0.0%
	1	46	877	9	36.8%	213	4	41.6%	5,284	138	33.8%
	2	35, 49	607	10	56.2%	133	4	63.6%	3,166	141	60.3%
	3	30, 45, 52	430	9	69.0%	92	4	74.6%	2,336	97	70.7%
	5	27, 36, 43, 50, 59	256	6	81.5%	48	2.5	86.8%	1,240	61	84.5%
	8	25, 29, 35, 41, 44, 49, 57, 66	135	4	90.3%	22.5	2	93.8%	591	51	92.6%
40	0	–	1,208	14	0.0%	318	6.5	0.0%	7,111	164	0.0%
	1	45	790	13	34.6%	192	5	39.6%	4,773	148	32.9%
	2	35, 49	531	9	56.0%	117	4	63.2%	2,869	136	59.7%
	3	29, 39, 51	394	7	67.4%	84	3	73.6%	1,900	88	73.3%
	5	27, 36, 44, 51, 59	232	6	80.8%	45	2	85.8%	1,203	69	83.1%
	8	25, 28, 35, 37, 46, 51, 57, 66	120	4.5	90.1%	19	1.5	94.0%	513	45	92.8%

45	0	–	1,084	12.5	0.0%	286	6.5	0.0%	6,606	160	0.0%
	1	37	701	10	35.3%	169	169	40.9%	3,794	108	42.6%
	2	34, 51	485	9	55.3%	107	107	62.6%	2,677	116	59.5%
	3	29, 40, 53	390	6	64.0%	83	83	71.0%	1,856	110	71.9%
	5	27, 32, 40, 49, 59	205	6	81.1%	37	37	87.1%	890	45	86.5%
	8	24, 29, 33, 37, 45, 50, 56, 67	108	4	81.1%	17	17	94.1%	445	39	93.3%
55	0	–	966	12	0.0%	260.5	6	0.0%	6,277	172	0.0%
	1	35	610	10	36.9%	144	4	44.7%	3,333	120	46.9%
	2	31, 42	412	6	57.3%	90	4	65.5%	2,113	122	66.3%
	3	29, 37, 46	361	6	62.6%	76	3	70.8%	1,612	80	74.3%
	5	27, 30, 39, 48, 51	180	5	81.4%	32	2	87.7%	845	65	86.5%
	8	25, 28, 30, 36, 40, 43, 51, 64	97	4	90.0%	15	1.5	94.2%	340	43	94.6%
Lifetime sustained immunity	0	–	918	12	0.0%	251	6	0.0%	6,218	176	0.0%
	1	35	553	9	39.8%	134	4	46.6%	3,263	85	47.5%
	2	31, 42	362	6	60.6%	81	4	67.7%	2,056	122	66.9%
	3	29, 37, 46	250	5	72.8%	53	2	78.9%	1,395	78	77.6%
	5	27, 30, 35, 45, 47	143	5	84.4%	26	1	89.6%	656	61	89.4%
	8	24, 26, 29, 32, 37, 42, 48, 52	72	4	92.2%	12.5	1.5	95.0%	275	36	95.6%

screening policies. The constructed screening strategies are particularly cost-effective for small numbers of lifetime screenings. They are more cost-effective than constant interval screening strategies. In particular, the constructed screening strategies can provide the same health benefits with substantially fewer screenings, false positives, and cancer treatments. All of these benefits result in a substantial reduction in costs and discomfort to the screened population.

4 Considerations and projections of screening strategies through optimization in a post-vaccination era

In recent years, there has been significant progress in understanding the natural history of cervical carcinogenesis and the causal role of oncogenic strains of the HPV virus. This has led to two vaccines that prevent the two major oncogenic strains of HPV (namely 16 and 18). These strains account for approximately 70% of all cervical cancers [9]. Note that 3.4% of women aged 14–59 have HPV 16/18 infections compared to 26.8% of women who have HPV infections [40]. Since the vaccines provide only a partial means of prevention against cervical cancer, it is essential that women continue cervical screening along with vaccination to provide the best possible prevention [26]. As a result, the proper timing of the screenings to maximize their effect towards preventing cervical cancer will continue to be of interest in the post-vaccination era. In fact, the potential benefits of screenings will decrease due to the reduced lifetime risk of cervical cancer after vaccination. So, the proper timing of the screenings may become even more important if screening efforts are limited. Furthermore, it is likely that vaccination will change the natural history of cervical carcinogenesis, especially if the vaccine is found not to have sustained lifetime immunity. Therefore, it is of interest to see how the optimal screening ages change at different durations of sustained vaccine immunity.

In this section, we perform an analysis on the potential impact of HPV 16/18 vaccination on cervical carcinogenesis and cervical cancer screening. We also examine the effect on the heuristic optimum screening ages that result from optimizations as the duration of sustained vaccine immunity changes. At present, there is great uncertainty about how long immunity is sustained in women who have been vaccinated against HPV. We perform the analysis by creating 45 screening scenarios with varying durations of sustained vaccine immunity and different numbers of available lifetime screenings.

4.1 Calibration and assumptions

The simulation model cannot project the natural history of cervical carcinogenesis after vaccination for the various

oncogenic strains of HPV. This is because the simulation model does not include the appropriate HPV states in the natural history of cervical carcinogenesis. By using the best available projections from the literature on the impact of the HPV vaccine and by considering the models used in those studies, we can calibrate the model to provide general insights into dynamic screening strategies through optimization in a post-vaccination era.

Given the lack of necessary data in the medical literature, we use two assertions from medical studies to make assumptions regarding the transition probabilities in the simulation model. First, vaccination is expected to reduce cancer incidence and cancer deaths by approximately 70% in the ideal scenario, since the vaccine is designed to protect against the two strains of cancer that cause 70% of cervical cancers [9, 26]. Second, protection from the HPV 16/18 strains lowers the progression transition probabilities from Well to CIN I and from CIN I to CIN II. We also assume that the progression probabilities of states CIN II onward and all regression transition probabilities stay the same [6, 9]. What cannot be ascertained, however, is the relative degree to which the transitions from Well to CIN I and from CIN I to CIN II are affected. This is because models used to study the vaccine also included transition probabilities to and from various HPV strain groups that capture the heterogeneous role of those strains groups towards carcinogenesis. To minimize error, we assume that both transition probabilities reduce at the same rate. Thus, a scaling factor $0 \leq \alpha \leq 1$ is introduced to the model for scaling the transition probabilities from Well to CIN I and from CIN I to CIN II so that cancer incidence is reduced by 70% in the case when the HPV vaccine prevents all infections from strains 16/18 and assuming that perfect immunity from the vaccine does not wane over time. This provides the transition probabilities from which to analyze the model immunization scenarios. However, the calibrated model has biased estimates of the prevalence levels of CIN I and CIN II at different ages, underestimating CIN I and overestimating CIN II.

Evidence from clinical trials suggests that immunity following vaccination exceeds 5 years and appears to be sustained [26]. It is a key unknown however, whether this immunity reduces over time. If immunity does reduce, we do not know when and how it will happen. In the absence of empirical evidence, we assume that it drops from full to zero immunity according to an exponential rate over a period of 5 years.

We analyze how the duration of sustained vaccine immunity affects the dynamic screening ages that result from optimizations. In addition, due to the reduced risks of cervical cancer after vaccination, the potential benefits of cervical screenings reduce as the negative effects on the performance of screenings increase (such as increased false positives rates). Such effects can potentially have negative effects on cervical screening, such as decreased compliance by the population and an increased fatigue and boredom within the cytology workforce [26]. Therefore, it is also of interest to see how the duration of sustained vaccine immunity affects the risks of cervical carcinogenesis and the timing of the screenings. With these objectives in mind, we created eight different scenarios where the vaccine sustains full immunity up to ages 20, 25, 30, 35, 40, 45, 55, and lifetime. Immunity falls with an exponential rate to zero immunity over a period of 5 years. We also consider a ninth scenario with no vaccination. Simulation-optimization was applied to these nine scenarios to generate screening strategies with 1, 2, 3, 5, and 8 available lifetime screenings that minimize cancer incidence. This creates 45 screening scenarios. Table 10 summarizes the results of all simulation-optimizations. We use the nine natural history solutions with no screening as the base cases.

4.2 Results and conclusions

The first observation is that there are diminishing returns on the health benefits of vaccination, as the duration of sustained immunity increases. This is because most HPV infections occur at younger ages, so extending the duration of sustained immunity has fewer opportunities to prevent HPV infections at older ages. Figure 4 shows diminishing returns on the proportion of cancer incidence that is reduced (in comparison to the base case of neither vaccinating nor screening). Note that vaccine efficacy up to age 12 captures the case of no vaccination, since that is the age when the CDC recommends vaccination [5]. For example, the vaccine achieves 50% of its full potential (of reducing cancer incidence and cancer deaths by 70%) if it has sustained immunity up to approximately 25 years of age. It achieves 75% of its full potential if it has sustained efficacy up to approximately 30 years age. The remaining 25% of its potential is actualized from 30 years of age onward. This is because the risks of HPV infection (and as a result the risks of CIN and cancer) are age dependent, as they are directly related to sexual patterns in the population.

As the duration of sustained vaccine immunity increases, it naturally leads to a reduction in the *absolute* benefits of screenings, since fewer immunized women develop cervical cancer. Table 10 reports the reduction in cancer incidence as well as the optimal screening ages for 0, 1, 2, 3, 5, 8 scheduled lifetime screenings. However, the *relative* benefits of screening is approximately constant as the duration of sustained immunity increases when compared to the fewer cancers in the base cases (with vaccination and without screening), as illustrated in Fig. 5. Figure 5 illustrates the relative reduction that is achieved for a specific number of available lifetime screenings when

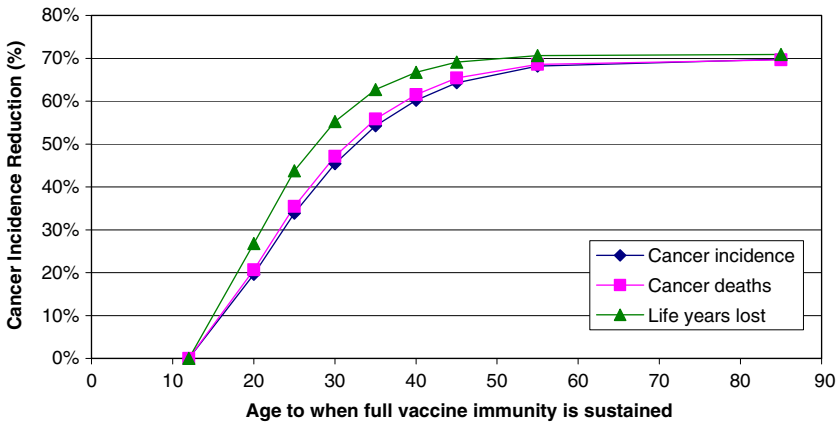

Fig. 4 Reduction in cervical cancer as a function of the age when full vaccine immunity is sustained compared to no vaccination

compared to the corresponding base case with no screening and the same duration of sustained immunity, as reported in Table 10. When the vaccine is not introduced, one lifetime screening averts 1,138 cancers per 100,000 (39% of the base case with no screening). With sustained vaccine immunity up to 25 years, one lifetime screening averts 808 cancers per 100,000 (40% of the base case with no screening and sustained vaccine immunity up to 25 years). With lifetime sustained immunity, one lifetime screening averts 365 cancers per 100,000 (40% of the base case with lifetime sustained vaccine immunity).

When the duration of sustained vaccine immunity increases, there are greater (though diminishing) benefits. This, however, paradoxically has the potential of having a negative impact on cervical screening, which needs to be continued as a supplement to vaccination due to the partial protection of the vaccine. The reduced lifetime risks of precancerous lesions and cancer will lead to a reduction of the benefits of cervical screening and an increase in false positive rates. This, as a result, has the potential in giving a negative perception to cervical screening to the screened population, which can eventually affect the performance of screening due to reduced compliance rates. As a result, the value of properly timing the screening ages for maximum effect maybe even greater in the post-vaccination era. As analysis in Section 3 indicates, properly timed screening strategies provide the same health benefits as constant interval screening strategies with substantially fewer screenings and fewer false positives, thereby counteracting the potential negative impact of vaccination towards cervical screening.

The introduction of a vaccine ultimately changes the natural history of cervical carcinogenesis. So it is of interest to see how the dynamic screening strategies are affected at varying the duration of sustained vaccine immunity. Figure 6 indicates the pattern in which the screening ages will be affected. The curve in Fig. 6 for one lifetime screening depicts how the optimum screening ages for one, two, and three lifetime screening change as the duration of sustained vaccine immunity increases. The optimum screening age with one lifetime screening without vaccination is 35. The optimum screening age occurs later,

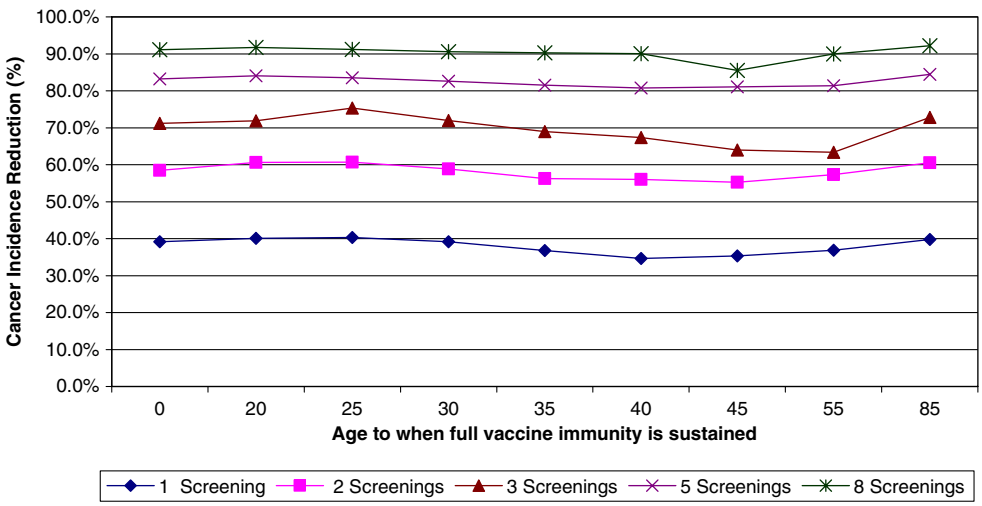

Fig. 5 Percentage of cancer incidence reduction with 1, 2, 3, 5, and 8 lifetime screenings as a function of the age when full vaccine immunity is sustained compared to the base case with immunization and without screening

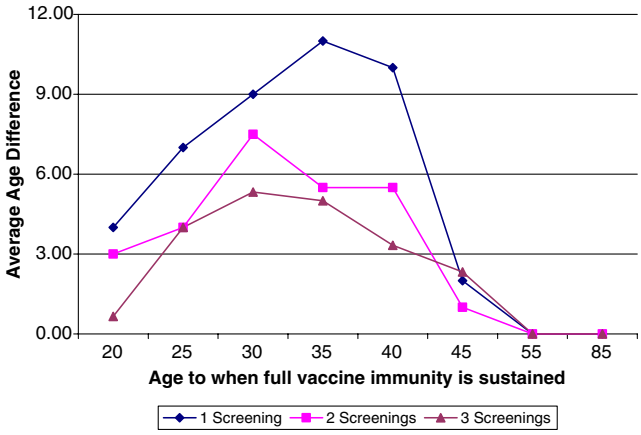

Fig. 6 Average increase in optimum screening ages as a function of the age when full vaccine immunity is sustained

reaching 46 years of age as the vaccine's immunity lasts up to 35 years of age. As the vaccine's immunity is sustained for longer periods the optimum screening age occurs earlier, eventually returning to 35 if immunity is sustained up to 55 years of age or older. This pattern is maintained for the heuristic optimum screening ages for all numbers of lifetime screenings tested. Initially, there is a shift toward screening at older ages until vaccine immunity is sustained up to 30 to 40 years of age. As the duration of sustained vaccine immunity increases, cancer at younger ages initially decreases at a faster rate than cancer at older ages. As the duration of sustained vaccine immunity extends beyond 40, then cancer incidence decreases at the same rate across all ages, which eliminates the benefit of screening at older ages. Figure 6 indicates this pattern by depicting the average increase of the heuristic optimum screening ages in ages for 1, 2, and 3, lifetime screenings. Screening strategies with 5 and 8 lifetime screenings also exhibit this pattern but for clarity purposes are not depicted.

Table 10 and Figs. 4, 5 and 6 indicate the surprising result that the changes in the optimum screening ages for women vaccinated against HPV are not dramatic. These results illustrate that risks of CIN I are higher in ages prior to the vaccine losing its immunity. There seems to be a perception, however, that in the post-vaccination era, screening is more important as a supplement to vaccination after the vaccine starts portraying waning immunity [26]. However, the results in this section suggest otherwise.

5 Concluding remarks

Cervical cancer is a leading cause of cancer related deaths among women. Due to the asymptomatic nature of the disease before its advanced stages, screening is a critical means preventing cervical cancer and reducing mortality and suffering from it. Since the risks for CIN and cervical cancer vary by age, we have applied simulation-optimization on models that simulate the natural history of cervical carcinogenesis. This maximizes the impact of screenings in preventing cervical cancer, by determining the optimal ages to perform them.

This paper demonstrates how simulation-optimization can be used to identify dynamic cost-effective screening strategies that are also practical to serve as screening policies. By performing one optimization for each number of available lifetime screenings from 1 to 22, we provide efficient and dynamic screening strategies for any given amount of resources available. Even though we perform three separate sets of optimizations (minimizing cancer incidence, cancer deaths, and life years lost), we construct one set of dynamic screening strategies with objective values that are not significantly different from the heuristic optimum objective values with respect to all three criteria.

Of particular interest are the results for optimal screening strategies with a small number of lifetime screenings. Given 100% compliance rates by the screened population, with just one lifetime screening available cancer incidence is reduced by 39%, and cancer deaths and life years lost are reduced by 45%. With just three lifetime screenings, cancer incidence, cancer deaths, and life years lost are all reduced by at least 70%. These results indicate that constructing such strategies through optimization for low to middle-income settings can provide substantial benefits. Hypothetical scenarios that capture the potential impact of HPV vaccination suggest that the most important ages for screening are not likely to be much different and that screening will continue to be important prior to the vaccine immunity waning. Even though the screening strategies provided in this paper are applicable to at least Western European countries and the United States, the primary goal of this paper is to serve as a prototype study to show how simulation-optimization can be applied to provide a range of efficient screening strategies for any given amount of resources available. More work can be done in this direction when considering more specific populations of interest or more specific questions about screening strategies.

Possible future work could be to repeat studies in the literature using this approach. Two such examples are the Goldie et al. [10] and Goldie et al. [11] studies that examine cervical cancer screening policies for low-resource settings. Another example is the Mandelblatt et al. [14] study that compares the cost-effectiveness of various screening strategies by considering alternative methods of screening to Pap smears, such as HPV DNA testing. With a specific population of interest, the proposed model could be used to determine more tailored, realistic screening recommendations. In addition, risk-based screening strategies, such as those considered in [17, 18] for other diseases, could be

used to evaluate the tradeoffs of allocating resources across risk groups.

Vaccination will ultimately change the natural history of cervical carcinogenesis, and hence, new screening policies will have to be considered in the long term [26]. Since the lifetime risks of developing cervical cancer will decrease, the health benefits of screening will also decrease. Using optimization to construct screening strategies can help with both issues. With respect to the altered natural history of cervical carcinogenesis, the simulation-optimization model adapts to the natural history in the post-vaccination era. Therefore, optimization will be able to play a key role in finding new screening strategies to be implemented in the future.

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