Chapter 19: Cost-effectiveness of cervical cancer screening

Sue J. Goldie a,∗, Jane J. Kim a, Evan Myers b

a Department of Health Policy and Management, Harvard School of Public Health, 718 Huntington Avenue, 2nd Floor, Boston, MA 02115, USA
b Department of Obstetrics and Gynecology, Duke University, Durham, NC, USA

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1. Introduction

While randomized controlled trials provide the most valid estimate of cancer screening efficacy, as they adjust for both known and unknown confounding variables, they pose several economic and practical difficulties. First, because only a small proportion of the population will develop the disease and realize a screening benefit, trials would require screening of very large populations to generate a measurable effect. Additionally, several decades of observation might be necessary from the time of initiating a program to when an effect on cancer incidence would be measurable. Furthermore, a randomized controlled trial of different screening strategies may not be considered an acceptable alternative if screening is already widely accepted as a standard of care. In the case of cervical cancer screening, it is unlikely that clinical trials will be performed that could adequately compare all the possible variations of screening and treatment and the follow-up cohorts of patients for the decades required to assess long-term mortality and quality of life outcomes. Thus, disease simulation modeling is undoubtedly necessary.

In the last two decades, several computer-based cervical cancer models have been developed to inform specific policy questions related to cervical cancer prevention. We and others have assessed the comparative cost-effectiveness of different screening strategies while explicitly considering such factors as the relative performance and costs of different screening tests, the tradeoffs between screening test sensitivity and specificity, the attributes of tests that might facilitate uptake, options to manage abnormal results, and the effectiveness of different treatments [1]. Quantitative cost-effectiveness results of model-based screening analyses can be challenging to compare directly. In part, this is due to (1) the choice of model and parameter assumptions, which vary depending on the nature of the study objective, (2) the uncertainty around estimates of costs and outcomes, as well as variability in the value of these parameters in different settings, and (3) the different perspectives taken by analysts (e.g., societal versus healthcare payer). However, once these variables are accounted for, results are far more comparable and several general themes can be identified consistently among studies.
This chapter will synthesize the findings from cost-effectiveness analyses (CEAs) that have focused on cytology-based cervical cancer screening and identify several qualitative themes [2–5]. Second, consistent findings from analyses that have considered HPV-DNA testing as a triage for equivocal cytologic abnormalities [6–11] and HPV-DNA testing as a primary screening test with or without cytology [7–9,11–13] will be described for countries with existing screening programs. Key themes from studies that have assessed noncytology-based strategies that enhance the linkage between screening and treatment and may be more feasible in developing countries [14–17] will be identified. Finally, a summary of the most important methodological challenges and high-priority areas deserving of analytic attention will be provided.

2. Prior CEAs in developed countries

The vast majority of published CEAs of population-based cervical cancer screening performed in the last two decades have focused on high-income countries. Consequently, they have addressed issues such as the choice of screening interval, ages for starting and stopping screening, enhancements to conventional cytology, and integrating HPV-DNA testing into cytology-based screening programs as a triage for equivocal cytology results or as a primary screening test for women over the age of 30. Several general themes emerge from multiple studies despite differences in modeling structure and assumptions. These can be summarized as follows:

- The cost-effectiveness of screening in the general population becomes increasingly less favorable as programs are intensified by screening more frequently than every 2–3 years and/or aggressively following equivocal or low-grade cytological abnormalities that are likely to regress. This occurs because for any given level of test sensitivity and specificity, costs increase almost linearly with shorter intervals while the incremental gains in benefits rapidly diminish. In most analyses in developed countries, screening intervals of 3–5 years usually fall within acceptable limits of cost-effectiveness ratios. Biennial and annual screening strategies have very high cost-effectiveness ratios, and are generally considered not cost-effective from a policy perspective. The high costs of frequent screening are due not only to the increased number of tests, but also the detection and treatment of more low-grade lesions which, in the absence of screening, would regress on their own without intervention.

- The majority of European countries recommend screening beginning between the ages of 20 and 25 years, and continuing every 3–5 years until age 60–65 [18]. These general policies have cost-effectiveness ratios that would be considered very cost-effective according to multiple suggested criteria for cost-effectiveness ratio thresholds (see Chapter 18; [4]). For these countries, priorities should be expanding coverage in the population by using new technology such as HPV-DNA testing in a cost-effective manner and deciding how a vaccine could be utilized given existing screening practices. In the US, screening strategies implemented in clinical practice are often incongruent with those recommended by clinical guidelines, which in turn, at least until recently, are not always the most cost-effective strategies. However, in recent years, consistent with findings from cost-effectiveness analyses, recommendations have shifted to screening less frequently, delaying the initiation of screening until 3 years after sexual debut, and considering cessation of screening for women over age 65 who have been regularly screened and are negative.

- There appears to be little benefit from beginning screening at a very young age, and there could be harmful consequences due to unnecessary colposcopy and other procedures. In most countries with existing screening programs, the recommended age of beginning cytology screening ranges from 21 to 25 [4]. In the US prior to 1992, most national guidelines recommended initiating cervical cancer screening with the onset of sexual activity or at age 18 [19]. An analysis that compared this recommendation to policies that delayed screening until 3 years after sexual debut showed delayed screening to be more cost-effective.

- For women who have undergone cervical cancer screening at regular intervals throughout their lifetime and have consecutive negative results, a policy that discontinues screening around age 65 is reasonable [20]. Benefits of screening (in terms of life-expectancy gains) in a well-screened cohort decline rapidly after age 65 because the risk of dying from cervical cancer is substantially reduced because of the natural history of the disease, a reduction in prevalence resulting from screening and treatment at younger ages, and increasing risk of death from other causes. The relative cost-effectiveness of continued regular screening in low-risk older women will somewhat depend on the screening frequency. For example, when screening intervals are three to five years, termination of screening at age 65 does not save many resources [21]. It should be noted, however, that where women have not previously been screened, screening at older ages is very cost-effective because there is a large risk of disease in older unscreened women.

- Strategies that employ screening tests with higher sensitivity than conventional Pap smears (e.g., liquid-based cytology with HPV-DNA testing to triage equivocal cytology results, enhanced cytology with computer-assisted imaging, primary screening with HPV-DNA testing in older women) without modifying the routine screening interval offer little incremental benefit but increase costs, and thus are associated with very high incremental cost-effectiveness ratios. For example, in an analysis of screening in the US, the magnitude of the life-expectancy gains for annual screening with HPV-DNA testing and cytology compared with biennial screening with those same tests was 4 hours. Accordingly, the incremental cost-
The effectiveness ratio exceeded $2 million per year of life saved (YLS) [12]. Regardless of the criterion used for a cost-effectiveness threshold (see Chapter 18), this strategy would not be cost-effective.

- Similar strategies with more sensitive screening tests do, however, appear cost-effective in the context of screening every 3–5 years. For example, studies in European countries have shown that strategies that utilize HPV-DNA testing to triage equivocal results in the context of conventional or liquid-based cytology every 3 or 5 years have cost-effectiveness ratios that fall below each country’s GDP per capita [7,8,22]. In the US, using HPV-DNA testing as a triage test for equivocal results or in combination with cytology every 2–3 years among women over the age of 30 was also found to be attractive compared to using cytology alone annually [9].

Most studies report that primary HPV-DNA testing, and combined cytology and HPV-DNA testing are associated with a greater risk of unnecessary colposcopy throughout a woman’s lifetime. The potential negative quality-of-life effects of screening with such a sensitive test are not easily measured, but these will be approximately proportional to the number of screening rounds, and thus will be greater in scenarios of frequent screening. The rate of unnecessary colposcopies is another reason to carefully weigh the relative harms and benefits associated with all screening frequencies using more sensitive tests. Similarly, using HPV-DNA testing as a primary screening test in young women in their 20s will undoubtedly lead to very high rates of screen-positives. The impact of even a small and transient disutility experienced from a false-positive result could be enormously influential at the population level. Better data on the impact of HPV-DNA status on quality of life, individual screening behavior, and sexual behavior are a priority.

- Small changes in specificity are very influential on cost-effectiveness in settings with frequent screening and aggressive follow-up strategies [23]. This trend is important since HPV-DNA testing has on average 20–30% greater sensitivity but about 5–10% lower specificity than Pap cytology for detecting high-grade lesions or cancer in studies based on combined testing of all women with both cytology and HPV-DNA test (see Chapter 20). This is shown in Fig. 1, which displays the impact of test specificity on total per-woman lifetime costs for different levels of population screening coverage for twice-in-a-lifetime screening (Panel A) and annual screening (Panel B) with HPV-DNA testing, compared to no screening. When screening is infrequent (Panel A) at 100% coverage, increasing specificity from 60 to 100% results in a decrease in cost of $7. With very frequent screening (Panel B) at 100% coverage, lifetime costs decrease by nearly $50 as specificity increases from 60 to 100%. Analyses were conducted using a previously-published model [15].

3. Prior CEAs in developing countries

There are fewer published studies that assess screening in developing countries [14–17,24]. In one of the earliest mod-
eling evaluations of cervical cancer screening programs in developing regions, Sherlaw-Johnson et al. [14] reported that the most efficient use of resources would be to concentrate screening efforts using cytology and HPV-DNA testing on women age 30–59 at least once per lifetime as such blanket screening would reduce the lifetime risk of cervical cancer by up to 30%. Results published since then, using data from Thailand and South Africa, were qualitatively similar [15,16]. Most early analyses did not include programmatic costs and focused on a single country, thus, limiting the generalizability of key findings.

Recently, Goldie et al. conducted a comprehensive assessment of the cost-effectiveness of novel cervical cancer screening strategies in five regions of the world with differing epidemiological profiles where conventional cytology screening programs have thus far not been sustainable [17]. Costs were assessed using primary and secondary data, and included direct medical, direct nonmedical, patient time, and programmatic costs. To facilitate a broad policy comparison between studies, assumptions were standardized by experts with experience in each country. Strategies differed by initial screening test, targeted age of screening, number of visits required (one, two, or three), and protocols for follow-up. Initial screening tests included visual inspection with acetic acid, cervical cytology, and HPV-DNA testing. Three-visit strategies included an initial screening test, a diagnostic work-up incorporating colposcopy and biopsy in women with positive results, and treatment of cervical intraepithelial neoplasia (CIN). Two-visit strategies incorporated initial screening followed by treatment of all screen-positive women, without evaluation by colposcopy. One-visit strategies (i.e., “screen and treat”) incorporated immediate treatment in screen-positive women. Outcomes included the lifetime risk of invasive cancer, years of life saved, and lifetime costs (international dollars).

In all five regions, lifetime cancer risk was reduced by approximately 25% with a single lifetime screen using either one-visit VIA or two-visit HPV-DNA testing targeted at women 35–40 years of age. This reduction was nearly doubled with strategies performed two or three times per lifetime. Although the average per-woman lifetime costs varied considerably, strategies were identified in all five countries that had incremental cost-effectiveness ratios less than each country’s per capita GDP (see Chapter 18). To place the results into the context of other public health interventions in developing countries, single-lifetime screening strategies were as cost-effective as hepatitis B immunization, second-line treatment for tuberculosis, and malaria prevention with bed nets [17].

In the analysis above, the cost-effectiveness results were most sensitive to loss to follow-up, targeted screening age, coverage rates, and the cost of care (surgical or palliative) for invasive cervical cancer. In addition, they found that the population-level impact of screening (i.e., reduction in the incidence and mortality of cervical cancer) was most influenced by the level of coverage.

Fig. 2 shows the impact of test sensitivity on reduction in lifetime risk of cervical cancer for different levels of population screening coverage for twice-in-a-lifetime screening (Panel A) and annual screening (Panel B), compared to no screening. See text for further details. Analyses were conducted using a previously-published model [15].
ing sensitivity has a greater impact when coverage is lower. For example, at 25% coverage, reduction in lifetime risk of cancer is 13% when increasing sensitivity from 60 to 100%, whereas at 100% coverage, reduction in cancer risk is only 4%.

Several general themes have been identified by studies focusing on resource-poor settings that have been unable to implement and support ongoing screening programs. These can be summarized as follows:

- For countries with limited resources, screening efforts should target women age 35 or older, and strategies should focus on screening all women at least once in their lifetime before increasing the frequency of screening. If high coverage can be achieved, screening two to three times per lifetime could reduce lifetime cancer risk by 25–40%. Targeting the appropriate age groups is crucial, generally around age 35 and then at 40 in the case of two lifetime screening tests; screening three times in a lifetime should occur between 30 and 50 years of age with spacing between tests of about 5 years.

- Results of published analyses show that the choice between cytology, HPV-DNA testing (most-effective), and visual methods (least costly), is most sensitive to the ability to link screening and treatment in fewer visits, the resources required with each test, and test sensitivity.

- When screening is only one to three times per lifetime, and if coverage rates are below 25%, enhancements to screening test sensitivity have minimal impact at the population level (e.g., increasing sensitivity from 60 to 100% provides an incremental reduction in the lifetime risk of cancer of less than 5%). However, provided widespread coverage can be achieved, small changes in sensitivity are more influential on population impact and cost-effectiveness in settings with infrequent screening, while changes in specificity are much less influential.

- In developing countries, within-country and between-country differences affect screening cost components to a greater degree than in resource-rich settings (see Chapter 18). The absolute level of cervical cancer mortality reduction is most sensitive (by far) to coverage rates, minimizing loss to follow-up of women with positive results, and long-term effectiveness of cryosurgery in screen/treat strategies, whereas the cost-effectiveness ratios are most sensitive to nonmedical costs (time and transportation) and the availability and cost of cancer treatment (see Chapter 18).

4. Overview of CEA results in all world regions

The need for a global perspective in a discussion of policies for cervical cancer prevention is made apparent by a comparison of the strategies used in very different settings. Fig. 3 shows the discounted lifetime costs and clinical benefits (expressed as reduction in the lifetime risk of cancer) of different screening strategies performed at different screening intervals. The cost-effectiveness of moving from one screening strategy to a more costly alternative is represented by the difference in cost divided by the difference in cancer incidence reduction associated with the two strategies. Strategies lying on the efficiency curve dominate those lying to the right of the curve (not shown) because they are more effective, and either cost less or have a more attractive cost-effectiveness ratio, than the next best strategy. For each strategy on the curve, a range of cost-effectiveness ratios and examples of countries in which cost-effectiveness analyses

![Fig. 3. Efficiency frontier depicting costs and benefits of screening strategies in different regions of the world [6–10,12,17,26]. Strategies differ by screening test (i.e., visual inspection using acetic acid (VIA), HPV-DNA testing, conventional cytology, and *liquid-based cytology with HPV-DNA testing to triage equivocal results) and screening frequency.](image)
were conducted are shown based on a review of the published literature. The slope between two strategies is steepest when the net gain in cancer incidence reduction is greatest (see Chapter 18). In this figure, strategies differ by screening test and screening frequency, ranging from once per lifetime to annual screening.

Strategies at the lower left of the curve are those which involve less technically intensive tests (VIA and HPV-DNA testing) and infrequent screening intervals (e.g., one to three times per lifetime). Such strategies, which have cost-effectiveness ratios ranging from $110 to $2500 per YLS, are considered to be attractive strategies for countries in poor regions of the world, such as India and Thailand [17].

Screening at 3- and 5-year intervals using conventional cytology produces cost-effectiveness ratios that range from $6800 to $25,600 per YLS based on analyses in European countries such as the UK, The Netherlands, France, and Italy [7,8,10], and 2-year screening with cytology ranges from $34,500 to $56,400 per YLS based on analyses in Australia and the US [6,9,12,26]. More aggressive strategies, such as screening every 2 years or annually using liquid-based cytology (with HPV-DNA testing for triage of equivocal cytology results), fall on the “flat of the curve” because they have much higher costs yet add very little benefit; these strategies, assessed mainly in analyses conducted to address clinical guideline questions in the US, range from $174,200 to over $1 million per YLS [6,9].

It is compelling to examine this figure in the context of the most pressing policy issues in developing versus developed countries. From a broad public health perspective we are reminded of the differences in the potential “value” of a single dollar invested where it is needed most (i.e., in developing countries) versus the “value” of a dollar invested in wealthy countries with existing screening. It is interesting to invert the incremental cost-effectiveness ratio to gain an insight into the differences between the most aggressive screening strategy shown on the graph (far upper right) and the least aggressive (far lower left). Expressing the incremental benefits relative to the incremental costs using a “benefit-cost ratio” would translate to 2.2 weeks of average life expectancy gain per $50,000 in the US. In contrast, in India, this would translate to a gain of 5000 years of life expectancy per $50,000.

5. Ongoing challenges

There will always be parameter and model uncertainty in each of the model-based analyses summarized here. Parameter uncertainty concerns the true values of the input parameters, whereas model uncertainty involves the way these parameters are modeled (or synthesized or manipulated to be appropriate for the model structure). Typically, models are calibrated to match data on age-specific cancer incidence and mortality, and, if available, prevalence of HPV and CIN. A limitation of this approach is that modelers are matching a cohort simulation to cross-sectional data. There may be substantial cohort effects that will affect cancer incidence and mortality, including exposure to HPV (age at sexual debut, average number of partners), exposure to factors which may contribute to increased cancer risk once infected with HPV (pregnancy, smoking, HIV), changes in competing risks (age-specific mortality from other causes, rates of hysterectomy for benign disease), changes in factors which affect diagnosis of cervical cancer (access to medical care, changes in endemic conditions, which lead to symptoms that mimic early cervical cancer), and changes in stage-specific survival from cervical cancer (improvements in treatments, reductions in morbidity and mortality associated with treatment). Ideally, age-period-cohort models could help address some of these issues, but the data necessary for construction of these models are not commonly available, especially in the developing countries where some of these secular trends may be most dramatic.

The choice of model structure will continue to be challenging. Cervical cancer natural history and screening models have evolved considerably in parallel with a better understanding of the role of HPV in cervical carcinogenesis, and as the policy questions become more complex, this process will need to continue. For example, analyses focusing on HPV-DNA testing as a primary screening test require additional sophistication in model structure to represent the detailed age-specific patterns of HPV positivity in women without cytologic abnormalities, with equivocal and low-grade abnormalities, and with high-grade disease. To assess newer screening strategies that diverge based on an individual woman’s history, we require first order Monte Carlo methods (see Chapter 18), which more easily allow the analyst to incorporate many dimensions of heterogeneity (e.g., type-specific HPV, individual-based risk factors such as HIV, parity, smoking, etc.), to reflect both variability and uncertainty in a more sophisticated manner and to permit the risk of a single event to depend on a series of past events. Models used for evaluating cervical cancer control strategies in developing countries must be able to accommodate more details regarding the operational delivery of screening and treatment services. Models that include vaccination strategies will need to either link with, or utilize parameters from, dynamic transmission models (see Chapter 21).

Finally, for analyses that address the critical questions about how screening test performance might change in the presence of a type-specific vaccination (see Chapter 20), the models need to fully represent HPV type-specific heterogeneity. The price of representing increasing complexity and heterogeneity of HPV types in a model of cervical carcinogenesis is that the number of “unobserved” natural history parameters quickly multiplies. Fortunately, epidemiologic data on age-related prevalence of type-specific HPV, age-related incidence of CIN and invasive cancer, and the distribution of HPV types within CIN and cancer are increasingly available. These data, together with formal calibration methods, can theoretically permit the development of a model that both respects our uncertainty regarding natural history but forces the model
to be consistent with multiple sources of epidemiologic data [27].

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**References**


