Second International Conference on Cervical Cancer

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Decision Science and Cervical Cancer

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Mathematical modeling is an effective tool for guiding cervical cancer screening, diagnosis, and treatment decisions for patients and policymakers. This article describes the use of mathematical modeling as outlined in five presentations from the Decision Science and Cervical Cancer session of the Second International Conference on Cervical Cancer held at The University of Texas M. D. Anderson Cancer Center, April 11–14, 2002. The authors provide an overview of mathematical modeling, especially decision analysis and cost-effectiveness analysis, and examples of how it can be used for clinical decision making regarding the prevention, diagnosis, and treatment of cervical cancer. Included are applications as well as theory regarding decision science and cervical cancer. Mathematical modeling can answer such questions as the optimal frequency for screening, the optimal age to stop screening, and the optimal way to diagnose cervical cancer. Results from one mathematical model demonstrated that a vaccine against high-risk strains of human papillomavirus was a cost-effective use of resources, and discussion of another model demonstrated the importance of collecting direct non–health care costs and time costs for cost-effectiveness analysis. Research presented indicated that care must be taken when applying the results of population-wide, cost-effectiveness analyses to reduce health disparities. Mathematical modeling can encompass a variety of theoretical and applied issues regarding decision science and cervical cancer. The ultimate objective of using decision-analytic and cost-effectiveness models is to identify ways to improve women's health at an economically reasonable cost. ***Cancer* 2003;98(9 Suppl):2003–8.**

KEYWORDS: cervix neoplasms, statistical models, decision theory, costs and cost analysis, health care economics, health policy.

Mathematical modeling and its use in guiding cervical cancer screening, diagnosis, and treatment decisions, both at an individual level and at the policy level, are proving useful to health care professionals seeking new tools to meet new demands in patient care. In recent years, mathematical models have proliferated as investigators have attempted to evaluate the effectiveness and cost effectiveness of clinical interventions.

At the Second International Conference on Cervical Cancer held at The University of Texas M. D. Anderson Cancer Center, the authors made individual presentations regarding the use of mathematical models, and those presentations are summarized here. Offering an overview of mathematical models and their applications were Evan R. Myers, Associate Professor at Duke University Medical Center in Durham, North Carolina, and Jeanne S. Mandelblatt, Professor of Medicine and Director of Cancer and Aging at Georgetown University Medical Center in Washington, D.C.

Mathematical Modeling and its Applications

The standard metric for proof of the efficacy of clinical interventions has been the randomized clinical trial; however, randomized clinical trials are not always practical, economically feasible, or ethically conscionable. For example, conducting a randomized clinical trial comparing Papanicolaou (Pap) smear testing every 3 years with screening every 5 years never could be accomplished. Physicians who recommend annual screening would not want their patients to participate, and the protocol violates the usual care recommendation to have Pap smear testing at least every 3 years after 3 consecutive tests with negative results. Thus, although policy may recommend testing at least every 3 years, such a policy could never be tested empirically. An additional argument may be based on feasibility regarding the statistical considerations in a randomized clinical trial. In particular, it would take many years to detect statistically significant differences in cervical cancer rates. Thus, such hypothetical comparisons can be performed only with the use of mathematical models.

Mathematical models can be constructed to simulate reality. Based on the best available data at the time of model construction, clinical mathematical models can answer questions regarding clinical decisions that need to be made. These clinical decisions can be based on considerations that arise in the individual patient setting (e.g., what is best for the patient) or on considerations from the public policy arena (e.g., the best allocation of economic resources to provide health care for a population of patients).

Mathematical models can answer questions regarding what parameters need better estimates, whether the work is basic research or epidemiological or clinical research. It is not uncommon for there to be a range of values for various parameters in a model (such as progression and regression rates for preinvasive disease). By varying these values across the reported range and comparing the effect of variation on model predictions, researchers using models can identify which parameters are most important in determining outcome. This, in turn, can help identify priority areas for epidemiological and clinical research. Quantitative estimates of the effect of variations in parameters on outcomes can assist with sample size calculations for these other studies. Models also can extend time horizons, for example, by examining extremely long development periods that would be difficult to examine in randomized, controlled studies. They also can estimate effects in subgroups of populations and tell what would be gained by targeting certain populations with, say, prevention efforts.

TABLE 1
Questions Regarding Cervical Cancer That May Be Answered Using Mathematical Models

- How often should we screen for cervical cancer? (Every third year? Every second year?)
- What is the value of a one-time screen?
- When should we stop screening for cervical cancer? (Should we stop at age 65? Age 75? Should we not stop at all?)
- What is the best method to screen for cervical cancer? (Papanicolaou smear? Should we use conventional cytology or quantitative cytology?)
- What is the role of HPV testing in the screening for cervical cancer?
- After an abnormal result is found at time of screening, what is the best method to diagnose cervical cancer? (Colposcopy? Optical spectroscopy?)
- What is the best way to treat high-grade squamous intraepithelial lesions?
- Are see-and-treat strategies a viable option?
- What are the best ways to deal with noncompliant patients (i.e., patients who may not appear for regular screening or who do not come to their follow-up visits after treatment)?
- How would the availability of a human papillomavirus (HPV) vaccine affect cervical cancer-related outcomes (costs, life expectancy, quality-adjusted life expectancy, cases of cervical cancer)?
- How would the availability of a HPV vaccine affect screening programs for cervical cancer?

Mathematical Modeling in Cervical Cancer

In the case of cervical cancer prevention and control, several mathematical models have been published over the past several years to identify best clinical practice and public policy.[1–10] New interventions for cervical precancer, such as fluorescence spectroscopy, also can be evaluated using mathematical modeling.[11]

Investigators have identified several important questions of interest regarding cervical cancer prevention and control (see Table 1). Previous decision-analytic models typically have focused on one or two of these questions. For example, Mandelblatt et al.[10] attempted to answer the questions regarding the frequency of testing and the question of when to stop screening. Kim et al.[9] attempted to answer the question about the role of human papillomavirus (HPV) testing in patients with Pap smear results indicating atypical squamous cells of unknown significance.

For an example of what a mathematical model can calculate, consider the work of Mandelblatt et al.[10] Constructing a randomized clinical trial to examine the clinical strategies evaluated by the model would not be practical. In the model, Mandelblatt et al. examined 18 possible strategies. The strategies consist of 3 possible times to end screening (age 65 years, age 75 years, and screen until death), 3 possible testing strategies (Pap smear, Pap smear plus HPV testing, and HPV testing alone), and 2 possible screening frequencies (every 3 years or every 2 years). If a randomized clinical trial were to be constructed from this model, then the sample size required to identify statistically significant differences would be enormous.

Using mathematical modeling to determine ex-

pected differences in outcomes from following hypothetical clinical strategies also may be useful for identifying parameters of interest in individual or policy decision making. These parameters may be of consequence when sensitivity analysis is performed, demonstrating that the parameters, if they are changed or improved, may switch the optimal decision. If additional data were obtained, then they could better clarify the role of that parameter in the decision making. Thus, mathematical models can justify subsequent research investigation meant to clarify the true value for a parameter of the mathematical model.

Decision-Analytic Models and Cost-Effectiveness Analysis

Decision-analytic models are special cases of mathematical models (see Table 2 for glossary). Mathematical models are quantitative representations of real-life situations. Decision-analytic models also are quantitative representations of real-life situations but are placed in a special context: a decision must be made. Decision-analytic models also have a criterion for determining what makes an optimal decision. In clinical decision analysis, such a criterion may be the maximization of the survival probability or the maximization of life expectancy. When quality-of-life issues factor into decision making, often quality-adjusted life expectancy, measured in quality-adjusted life years (QALYs), is the outcome measure that is maximized for a decision-analytic model. Here, 1 QALY is defined as 1 year in perfect health. Years that are in less than perfect health are adjusted to some fraction of 1 year, in which smaller fractions represent poorer health.

Cost-effectiveness analysis often is modeled as a decision-analytic model with two outcome measures: cost and effectiveness. For each clinical strategy that is considered, the expected cost and the expected effectiveness (e.g., life expectancy or quality-adjusted life expectancy) are calculated. Clinical strategies that are cheaper and more effective than other strategies are said to dominate other clinical strategies. However, it is often the case that one strategy is more effective yet more costly than another; it is in this case that the incremental cost-effectiveness ratio must be calculated as the difference in cost divided by the difference in effectiveness of the two strategies.

The incremental cost-effectiveness ratio can be used as a means of comparing clinical strategies across diseases and health care interventions to determine the relative cost effectiveness of the clinical strategies. Strategies that have an incremental cost-effectiveness ratio below a predetermined threshold are then said to be cost effective. Strategies that have their incremental cost-effectiveness ratio above a predetermined threshold are then said to not be a cost-effective use of health care resources. Details of dominance and evaluating the results of cost-effectiveness analysis can be found in the report by Cantor.[12] No specific threshold has been established, although references have been made to threshold cost-effectiveness ratios between $20,000 and $100,000 per QALY.[13,14]

TABLE 2
Glossary of Medical Decision-Making Terms

Cost-effectiveness analysis: a method for comparing clinical strategies that evaluates their economic costs against their health effects
Decision analysis: a formal, structured, quantitative methodology for studying decision problems characterized by uncertainty
Dominance: in cost-effectiveness analysis, the situation in which one clinical strategy is both less expensive and more effective than another strategy
Incremental cost-effectiveness ratio: in cost-effectiveness analysis the difference in costs divided by the difference in effectiveness in a comparison of two strategies. The incremental cost-effectiveness ratio is a measure of the additional cost needed to gain an additional unit of effectiveness. The usual metric for cost-effectiveness analysis is *dollars per quality-adjusted life year*.
Markov model: a mathematical simulation that consists of recurrent states. In clinical decision analysis, these states are known as health states.
Non–health care costs: costs, in addition to time costs, that would be added to direct health care costs when performing a cost-effectiveness analysis from the societal perspective. Direct non–health care costs can include transportation, parking, babysitting, and costs for unpaid caregiver's assistance.
Quality-adjusted life year: a period of time in perfect health that is equivalent to 1 year in a state of ill health
Threshold: the point at which the optimal decision would change
Time costs: costs of time seeking medical care. These costs, in addition to non–health care costs, would be added to direct health care costs when performing a cost-effectiveness analysis from the societal perspective.

Part of the challenge in decision-analytic models is recognizing that the expected differences in outcomes may be very small among the alternative strategies. These have been referred to in the literature as "close calls" or "toss-ups".[15] First, it is important to make the point that the results of decision-analytic modeling do not require statistical significance for there to be a determination of an optimal result. The context for decision analysis is that a decision needs to be made; and, if criteria have been established for determining an optimal result (e.g., maximization of quality-adjusted life expectancy), then the strategy that satisfies the decision-making criteria is best. Sensitivity analysis can and should be performed to test whether the selected decision remains optimal under different circumstances. Sensitivity analysis, as discussed above, is the process by which parameters of the mathematical model are varied to determine whether the selected decision remains optimal in spite of variation in the model parameters.

A specific example of the use of a decision-ana-

lytic model to develop policy was presented at the conference by Gillian D. Sanders, Ph.D., an Assistant Professor at Stanford University (see Sanders and Taira[16]). Two options were considered: the use of a vaccine against high-risk strains of HPV and the usual care strategy (no vaccine). The model of McCrory et al.[7] was modified to incorporate the possibility and effectiveness of a vaccine for high-risk strains of HPV. Specifically, Sanders created a Markov model with several discrete health states, which included *well*, *presence of HPV*, *presence of squamous intraepithelial lesions*, *cervical cancer*, and *death*. In clinical decision analysis, a Markov model is a representation of a clinical situation in which a risk of an event repeatedly occurs over time.[17] Transition probabilities were based on data obtained from the literature. The natural history of HPV and cervical cancer were based on work done by the Duke Evidence-Based Practice Center.[7] This was a cost-effectiveness analysis; thus, model outcomes were expressed in terms of dollars per QALY. Implementation of a vaccine with 75% effectiveness against high-risk strains of HPV led to more costs but greater quality-adjusted life expectancy. Specifically, the incremental cost-effectiveness ratio of the HPV vaccination strategy compared with no vaccination was $16,135 per QALY gained. Compared with other clinical interventions, vaccination can be considered a cost-effective use of health care resources (with the threshold for cost-effectiveness typically estimated at $50,000 per QALY gained). Sensitivity analysis showed that the optimal decision to vaccinate was robust to variations in the model's parameters, including the efficacy of the HPV vaccine and cost of the vaccine. Sanders concluded that prophylactic HPV vaccination is cost effective, even at low efficacies. Even though the individual gains in quality-adjusted life expectancy are modest (6.2 days), the population benefits may be substantial.

Effectiveness and Cost Outcome Measures

In all cost-effectiveness analyses, it is critical to identify appropriate outcome measures of effectiveness and cost. Effectiveness, as discussed above, focuses on clinical outcomes. These can include survival, life expectancy, quality of life, or quality-adjusted life expectancy. Cost components often are more challenging to define, because the *perspective* of the analysis determines which costs are to be incorporated. The societal perspective is the most comprehensive perspective; however, an institutional perspective or patient perspective often may be more appropriate for analysis. Luce et al.[18] identify four components of costs that may be included as costs: 1) direct health care costs, typically the substantial component of health care interventions; 2) costs of resources not directly related to health care, such as babysitting or transportation; 3) costs for unpaid caregiver's assistance; and 4) cost of seeking medical care. These last three components typically are more challenging to collect in a cost-effectiveness analysis than direct health care costs, which were the subject of a presentation by Scott B. Cantor, Ph.D., a decision scientist at The University of Texas M. D. Anderson Cancer Center.

Cantor demonstrated the importance, methodology, pitfalls, and actual data from the collection of costs other than direct health care costs.[19] The U.S. Panel on Cost-Effectiveness in Health and Medicine created guidelines for a reference case for the performance of cost-effectiveness analysis.[20–22] These guidelines include the recommendation for performing cost-effectiveness analysis from the societal perspective (i.e., incorporating all possible factors that could impact the changes in costs and health from all entities who would be affected by the clinical intervention under study). Cantor demonstrated some of the nuances of collecting direct non–health care cost and time cost data. These costs are considered secondary to the direct costs of health care. They may include babysitting, elder care, transportation to the site of the health care provider, and time missed from work.

These difficulties may be overcome by soundly applying the principles of economic theory, which, at their core, identify the opportunity costs involved. The concept of opportunity costs is that, when an expense is incurred, a conscious decision is being made to spend resources (money or time) on one thing and to forego spending resources (money or time) on something else. Alternatively, opportunity costs can be defined as the costs of resources consumed expressed as the value of the next best alternative for using these resources.[23]

Cantor then went on to show the direct non–health care costs and time costs that were incurred in a population of women who participated in a clinical trial evaluating the effectiveness of alternative technologies for the screening or diagnosis of cervical precancer. In this sample of women, those who participated in the screening portion of the trial had costs that totaled $51.51, and those who participated in the diagnostic portion of the trial had costs that totaled $63.90.[19] The greatest portion of these costs came from time missed from work, which was estimated on the basis of median wage rates. Actual opportunity costs from time missed from work could have been

much larger, based on the sociodemographic characteristics of the patients who participated in the study.

It is possible that the direct non–health care costs and time costs for the screening or diagnostic patients do not seem substantial; however, when placed in the context of cost-effectiveness analysis for the screening and diagnosis of squamous intraepithelial lesions, these amounts may make an important contribution in the cost-effectiveness analysis. Previous studies that analyzed various strategies for the screening and diagnosis of cervical lesions typically expressed the effectiveness outcomes in terms of QALYs and carried out the results to several decimal places. If differences in quality-adjusted life expectancy exist that are 0.001 QALYs different, then an additional $50.00 divided by 0.001 QALYs yields an incremental cost-effectiveness ratio of $50,000 per QALY. This amount indeed is substantial in cost-effectiveness analysis.

Using Mathematical Models to Change Policy and Decrease Health Care Disparities

Mathematical models can affect health care policy as well as individual patient care decisions. In the final presentation, health economist Marianne C. Fahs, M.D., M.P.H., professor in the Health Policy Research Center, Milano Graduate School, New School University, discussed using mathematical models to influence policy and decrease health disparities using cost-effectiveness analysis. The mathematical models can be used to determine the optimal organization of a health program to maximize the health benefits for a finite expenditure of resources.[4] Fahs discussed three main criticisms of the current models of cost-effectiveness analysis that may lead to biased and inefficient policies. These included 1) dilutional effects, which are sensitive to prevalence and incidence rates; 2) utilization effect, in which models assume 100% utilization, which typically is untrue in reality; and 3) a cost-shift effect, in which a transfer of medical costs occur (e.g., in-kind home care, market-based vs. babysitting or day care).

First, regarding *dilutional effects*, it is well known that cost-effectiveness analyses that consider average-risk populations will yield different results from targeted analyses of high-risk populations. Often, these above-average prevalence rates among high-risk communities drive the favorable cost-effectiveness results of national analyses for the general United States population. Policy makers responding to these analyses seem justified in addressing policy changes to general populations, a consequence of the *dilutional effect*. Policies based on general population models (such as Medicare benefits for cervical cancer screening) that increase (or, in other instances, decrease) access to screening programs for general populations, rather than policies that target screening and treatment services to the underserved, will be inefficient.

For instance, in the first national cost-effectiveness analysis of cervical cancer screening in the U.S., which included targeted subanalyses of urban, low-income elderly women, Fahs et al.[3] found results for high-risk populations that differed notably from those obtained in analyses of general population groups. Based on prior work by Mandelblatt and Fahs,[1] the national analysis found that a preventive screening program among general populations was cost effective; that is, it saved years of life within accepted levels of screening program expenditures. However, among low-income elderly women, a targeted program would both add years of life and reduce cervical cancer-related health expenditures.

These findings were among the first to show that the benefits from some prevention programs for urban high-risk populations can outweigh the costs. Such cost-effectiveness analyses can influence important and costly policy changes.[22] Medicare policy changed to include preventive screening benefits for cervical cancer, responding in part to the results of this Congressionally mandated analysis. However, the new Medicare benefits were directed not toward increasing targeted programs for high-risk women but, rather, toward increasing access for general populations. Thus, the *dilutional effect* of general population cost-effectiveness analyses can have the adverse consequence of justifying policies that result in increased health expenditures without the increased life expectancy predicted by the models.

Second, the *utilization effect* occurs when national economic prevention policy models prepared for legislative consideration are required by Congress to assume 100% utilization in the estimates. This requirement has been justified for reasons of comparability with other analyses and for ethical reasons (Medicare, for instance, is not a means-tested federal insurance program). However, without follow-up and outreach programs geared to urban populations, utilization surely will not be 100%. Cost-effectiveness analyses that do not take these characteristics into account are based on inaccurate models of care and will lead to biased estimates, a *utilization effect*, and thus, biased policy conclusions.

Third, the *cost-shift effect* can have the adverse consequence of shifting the economic burden to patients and their caregivers if preventive interventions decrease the cost-effectiveness ratio by reducing market-based expenditures but result in an increase in family or caregiver time burdens. Fahs acknowledged the important work being undertaken by Cantor in

addressing the patient and caregiver nonmarket time costs. It is only through the explicit measurement of treatment-related patient and caregiver time costs that such potential *cost-shift effects* can be addressed.

Fahs concluded that many of the factors that crucially affect the results of cost-effectiveness analyses vary by age, race, and socioeconomic status. The need to understand the relations between health investments, health outcomes, and costs remains compelling within the complex environment of health care. Blanket policy statements based on the results of a cost-effectiveness analysis for general populations may result in biased prevention policies that effectively discriminate against vulnerable subgroups of the population. In her presentation, Fahs recommended that broader models of health care provision should be developed to incorporate all aspects of the health care system. There is an immediate need, Fahs asserted, for a balanced appraisal of the main issues affecting the results of cost-effectiveness analyses for preventive services policy for the heterogeneous populations of vulnerable individuals in our increasingly diverse society.

Summary

The five presentations on decision science and cervical cancer had a unifying theme of employing mathematical modeling for the purposes of evaluating and enhancing the screening, diagnosis, and treatment of cervical cancer. Both individual and policy decisions can be enhanced by learning from modeling, especially when clinical trials are not feasible, practical, or ethically conscionable. The details of the modeling can get fairly sophisticated, but this level of detail may be required to reflect the reality of the clinical and economic situation. The ultimate outcome of decision-analytic and cost-effectiveness models is to improve women's health at an economically reasonable cost.

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