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Development of a Stochastic Simulation Model of the Cost-Effectiveness of Promoting Breast Cancer Screening

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**Development of a Stochastic Simulation Model of the Cost-Effectiveness of Promoting Breast Cancer Screening**

Nicole Urban, Ph.D.

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Seattle, Washington 98104

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The purpose of this four-year project is to develop a comprehensive stochastic simulation model of the effectiveness and cost-effectiveness of breast cancer screening, including efforts to promote breast cancer screening. Emphasis in the first year was on model development including enhancement of an existing computer program to facilitate its use for the breast cancer model, specification of model components, review of the literature on cancer modeling, development of methods for unbiased estimation of years of life lost attributable to late-stage detection of breast cancer, and requesting necessary cost data. Year two will be spent finalizing the disease progression model, finalizing the data items to be used in the model, and procuring and analyzing data. The estimates generated from data analysis and assumptions from literature review will be incorporated into the model, and a report reviewing existing models and assumptions for assessing cost-effectiveness of breast cancer screening and estimating potential years of life saved attributable to screening will be developed. In addition, a report on the cost-effectiveness of alternative breast cancer screening strategies will be developed.
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Introduction

The purpose of this four-year project, funded in April 1994, is to identify an efficient strategy for reducing breast cancer mortality through breast cancer screening. To identify such a strategy, the trade-off between the frequency of screening among participants and the promotion of participation among underusers will be investigated. Ways to improve the effectiveness of screening in women aged 40-49 will be investigated, using new biomarkers and detection modalities, and the relative cost-effectiveness of various interventions to promote the use of regular breast cancer screening among women aged 50-80 will be investigated. A comprehensive stochastic simulation model of the effectiveness and cost-effectiveness of breast cancer screening will be developed, and its key parameters estimated.

Body

Emphasis during Year 01 was on planning and development of the model, and adapting the existing ovarian cancer model for use in the breast cancer project. Specific activities included: 1) enhancement of the model to account for benign tumors, competing mortality, and lack of independence among screening modalities, 2) review of the clinical aspects of breast cancer, 3) specification of model components, 4) recruitment of a mammographer to act as a consultant (without pay) as the model is developed, 5) literature review and presentations by investigators of the existing models, and their appropriateness for the purpose at hand, 6) methodologic work involved in estimating years of life saved, and 7) submitting a request for the SEER-Medicare data to the Health Care Financing Administration. Details of each aspect of the Year 01 work are described below.

Enhancement of the model

An existing stochastic simulation model of ovarian cancer screening is being adapted for use in the breast cancer project. Several limitations of the ovarian cancer model were addressed, in order to facilitate its use in the current project. The first change to the model was incorporation of competing mortality with respect to both screening and survival. If an individual dies from a competing cause prior to the end of the screening period, then screening stops for that individual and screening costs are no longer incurred in the model. Competing mortality has also been incorporated with respect to survival because it is implicitly accounted for in the Kaplan Meier survival distribution, which is generated from death regardless of cause.

Because benign tumors affect the false positive rate of screening tests, the model was refined to take into consideration the incidence of benign tumors and their relationship to false positive tests. Using the revised version of the model requires reviewing the literature to obtain estimates of the probability of benign tumors occurring and the probability of a positive test given a benign tumor, because in the model, false positives are generated based on these probabilities. This refinement of the model is important because it is the mechanism used to account for lack of independence among screening modalities, including mammography, clinical breast exam, and self-breast exam with respect to false positives. The assumptions made regarding the relationship of benign tumors to false positive screens will be validated by soliciting clinical expertise.
There is also a lack of independence among screening tests with respect to sensitivity, the ability of a test to detect an existing cancer. This is being handled by considering specific histologies, such as lobular carcinoma, separately.

Review of the clinical aspects of breast cancer

Specific work on modeling breast cancer began with literature review and presentations on breast cancer by Charles Drechsler, MD, a consultant on the project. The intent of this process was to provide the group with a basic understanding of both breast cancer and the anatomy of the breast as a foundation for more detailed work in modeling the disease and the screen. The presentations given covered the anatomy of the breast, breast cancer screening, mammographic abnormalities, detection of abnormalities by mammography, and an overview of breast cancer including risk factors, natural history, histological types, and prognostic factors.

Specification of model components

The components of the breast cancer model were specified through the development of a high-level flowchart defining the broad areas the model would address, as well as the generation of a specific list of the minimum data items required to develop the initial breast cancer model. The flowchart and list of data items are included as Appendices A and B.

Recruitment of a mammographer to participate in research team

Review of each of the model components resulted in the development of a list of questions about mammography to be addressed by the research team. Some of the topics identified by investigators are: 1) the factors that may affect the sensitivity of mammography including the mammographer’s experience, patient age, menopausal status of the patient, whether or nor a post-menopausal patient is on hormone replacement therapy, and histology, 2) the relationship between disease progression and the sensitivity of mammography, 3) the relationship between disease progression and age, 4) the relationship of breast density to age, and 5) the relationship of disease progression to the presence of calcifications on the mammogram. For a detailed understanding of each of these questions and others that arise during the modeling process, it was agreed that the guidance of an experienced mammographer would be useful. At Dr. Urban’s request, Dr. Harold Shulman of Talbot Road Radiology in Renton, Washington, agreed to attend regular meetings and provide clinical expertise.

Review of existing models

Each member of the research team assumed responsibility for review and presentation of one of the existing models of cancer screening. For each model discussed, the presenter reviewed the attributes of the model, its uses, the data required, the limitations of the model and the assumptions on which the model relies. A formal review of existing computer models is being conducted by Ruth Etzioni, PhD, a Co-Investigator on the project. This review work will be relevant as the breast cancer model is developed.

Special attention was given to the MISCAN model, the most sophisticated stochastic simulation model of breast cancer screening revealed by the literature review. As a result, investigators are maintaining regular communication with Rob Boer, who works on the MISCAN model in the Netherlands. Mr. Boer traveled to Seattle in March of 1995, and met with the project team to
share his group’s approach to cancer modeling, and to discuss in detail how the two groups approach particular issues around modeling such as disease progression and survival. Plans for collaboration include cross-validation as appropriate.

Methodologic work on estimation of years of life saved. Drs. Etzioni and Urban have begun work on development of an algorithm for use with the SEER data to obtain an unbiased estimate of the years of life lost attributable to detection of cancer at late rather than early stage, using Kaplan-Meier estimation techniques. Biases which must be avoided include length biased sampling and lead time bias. The prevalence of screening in each year must be taken into account in obtaining an unbiased estimate, because the SEER data do not represent an unscreened population.

Request for data

A formal request for the linked SEER-Medicare files was submitted to the Health Care Financing Administration in January 1995. The data have not yet been made available, but are anticipated by December 1995.

Conclusion

The upcoming year will be spent finalizing the disease progression model, finalizing the data items to be used in the model, and procuring or estimating the information needed for the model. The estimates generated from data analysis and assumptions from literature review will be incorporated into the model. Reports will be prepared describing the review of existing models and assumptions for assessing cost-effectiveness of BCS, and methods for estimating Potential Years of Life Saved attributable to screening. In addition, a report on the cost-effectiveness of alternative breast cancer screening strategies will be developed.
Appendix A

Components of the Model

Each component represents an area where the group needs to either: 1) make a preliminary decision, or 2) identify and assign tasks (such as literature review) requiring completion prior to making progress/decisions.

**Modeling Disease Progression**
Options for Modeling Disease Progression:
1) Stages
2) Model size of mass, nodal involvement, calcifications, and...what else?
3) Pre or post cure point (like MISCAN)

**Need to Model in terms of:**

- **Factors that Affect Survival**
  - Options for data sources:
    1) SEER data
    2) Clinical trials data
    3) Other
  - What does survival depend on?
    1) Stage specific survival like OVCA model?
    2) Other factors?

- **Factors that Affect the Screen**

**Modeling the Screen**
How does screen detect tumor?
How to model the sensitivity of mammography? As a function of breast density? Calcifications? What other factors affect sensitivity? Are there data on those factors? How to model false positives?

**Modeling Follow-Up for the Screen**
1) Additional views
2) Ultrasound
3) Short Interval FU
4) Biopsy
5) Other

**Modeling Treatment**
Do we want to model treatment for cost purposes?
Treatment Options:
1) Surgery
2) Radiation Therapy
3) Mastectomy
4) Lumpectomy
5) Other (Bone Marrow Transplant)
Appendix B

Data Inputs for the Ovarian Cancer Model and Breast Cancer Model

<table>
<thead>
<tr>
<th></th>
<th>Ovarian</th>
<th>Breast</th>
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<tbody>
<tr>
<td>cohort size</td>
<td>1,000,000</td>
<td>1,000,000</td>
</tr>
<tr>
<td>testing period (in months)</td>
<td>360</td>
<td>360</td>
</tr>
<tr>
<td>testing interval (in months)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>start age (years)</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>end age (years)</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>competing mortality</td>
<td>50-54 0.003509</td>
<td>55-64 0.009047</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65-74 0.020561</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75-80 0.051733</td>
</tr>
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Cancer model:

<table>
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<tr>
<th></th>
<th>Ovarian</th>
<th>Breast</th>
</tr>
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<tbody>
<tr>
<td>number of breast cancer stages</td>
<td>4 (actually 3)</td>
<td>3</td>
</tr>
<tr>
<td>number of breast cancer attributes</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>stage lengths (relative to stage 1)</td>
<td>0.5, 1.333, 0.333</td>
<td></td>
</tr>
<tr>
<td>stage lengths log normal distribution means</td>
<td>9, 4.5, 12, 3</td>
<td></td>
</tr>
<tr>
<td>survival data (SEER)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>life expectancy data (SEER)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>post- detection survival return to normal</td>
<td>15 years</td>
<td>15</td>
</tr>
<tr>
<td>prob. of breast cancer during testing period</td>
<td>0.0121</td>
<td></td>
</tr>
<tr>
<td>prob. of age groups at clinical detection</td>
<td>50-54: 0.153</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55-59: 0.184</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60-64: 0.202</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65-69: 0.179</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70-74: 0.150</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75-80: 0.132</td>
<td></td>
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<tr>
<td>exact age within age group at detection</td>
<td>uniform random</td>
<td></td>
</tr>
<tr>
<td>prob. of stage at clinical detection</td>
<td>1: 0.223</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2: 0.153</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3: 0.624</td>
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<tr>
<td>point in stage at clinical detection</td>
<td>0.5 of stage length</td>
<td></td>
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<tr>
<td>stage length distribution</td>
<td>log normal(9, 4.5)</td>
<td>uniform</td>
</tr>
<tr>
<td>prob. of benign tumor (incidence)</td>
<td>0.019, 0.010, 0.006</td>
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Screening model:

- mammogram sensitivity rate
- mammogram asymptomatic specificity rate
- mammogram delay distribution
- mammogram delay truncation range

self breast examination sensitivity
self breast examination specificity
self breast examination delay distribution
self breast examination delay truncation range
clinical breast examination sensitivity
clinical breast examination specificity
clinical delay distribution
clinical delay truncation range

Hypothetical serum test (1 is test a/b; 2 is ca125):
serum1 benign specificity rate
serum1 asymptomatic specificity rate
serum1 sensitivity
serum2 distribution
serum2 lam
serum2 log A
serum2 e (error)
serum2 d (duration)
serum2 level cutoff
serum2 false positive rise
serum2 rise criteria
serum2 benign tumors who act like mal.

Cost calculation:

discount rate (annual) 0.05
base year 1990
treatment cost data (annual) (SEER Medicare file)
cost (charge) of mammogram
cost (charge) of self breast examination
cost (charge) of clinical breast examination
cost (charge) of serum test