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in Assessing Treatment Alternatives for Lobular Carcinoma
in Situ

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13. The present project was designed to utilize existing longitudinal databases documenting risk of invasive cancer associated with Lobular Carcinoma <i>in situ</i> (LCIS) as well as newly collected data on quality of life associated with treatment options, to develop decision models for the treatment of premenopausal women diagnosed with LCIS and otherwise benign biopsy findings. Treatment options consisted of preventive bilateral mastectomy versus "watch and wait" with intensive screening. Analysis of a 22 year prospective, longitudinal database provided by the Connecticut Tumor Registry suggested that the risk of invasive cancer associated with LCIS might be significantly lower than has been suggested in retrospective studies of older data. Results of this study suggested that consideration of treatment for LCIS would be warranted only in women aged 45 years and younger. Decision analysis performed for women 40 and 45 years old, using estimates from the CT Registry as well as quality of life adjustments derived from a study of 212 medical students, preferred no surgery by a margin of approximately 5 years of life. Findings of this investigation strongly suggest that the risks assumed to be associated with LCIS as a marker for invasive cancer be reevaluated through comparisons with other recent, prospective data.			
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FOREWORD

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I. Introduction and Significance of Study

Most likely, the significance of Lobular Carcinoma *in situ* (LCIS) lies in its potential as a marker for invasive breast cancer in premenopausal women, a marker which can assist in identifying and preventing cases of invasive cancer and associated mortalities. However, since its identification in 1941 (Foote & Stewart), questions remain unresolved about the role of LCIS in the development of invasive cancers. While researchers increasingly agree that LCIS is a “marker” for increased risk of invasive breast cancer found primarily in premenopausal women (e.g., Ottesen et al., 1993), investigations have revealed equivocal results regarding the estimates of increased risk, as well as time to development of invasive disease should it occur.

A meta-analysis done by Bradley et al., (in Abeloff et al., 1993) included all reports available (N=13) in the LCIS literature of cases treated with some form of surgery, from local excision to preventive (bilateral or unilateral) mastectomy. In the thirteen reports reviewed, 391 women treated with mastectomy and followed an average of 10 years showed a “recurrence rate” of 2.7% and an associated mortality of .9% at 10 years. For patients in whom local excision alone was used, 389 patients, recurrence rate was 16.4%, with mortality of 2.8% at 10.9 years. The difficulty with this meta-analysis is that with many studies of LCIS, there has been little agreement on the inclusion of patients with prior or coexisting conditions (see critique by Kinne, 1992), such as prior invasive cancer in the contralateral breast or a combination of LCIS and Ductal Carcinoma *in situ* (DCIS). Given these difficulties, results of meta-analysis are not particularly useful for deriving risk estimates which might be used to drive clinical management of patients with LCIS alone.

The present research was designed to accomplish the following tasks:

1. To develop a formal decision model which would best reflect the choices in clinical management and their potential outcomes for women diagnosed with LCIS alone.
2. To critically evaluate existing databases and previous studies which contain information regarding the clinical course of women with LCIS, in order to derive optimal parameter estimates and realistic ranges for risk estimates and time frames to be included in the decision model.
3. To incorporate not only estimates of objective risks, but also subjective values, into final decision models. These subjective values provide quality of life adjustments (QUALY'S) for each outcome in a decision tree.

This investigation was designed to pave the way for decision analysis, using multiple, interrelated measures of outcomes, as a tool for helping the patient/physician team to arrive at the optimal course of action for each individual case; as well as a tool for arriving at more broad-based decisions regarding clinical management of LCIS which take into account more fully the risks and benefits of alternate courses of clinical action. During the course of this project, more emphasis was placed on data analysis than had been anticipated. This was due largely to the very valuable data provided by the Connecticut Tumor Registry, which called into question some of the critical assumptions existing literature would have the reader make.

Results of this investigation serve the essential purpose of demonstrating the usefulness of a complex decision model; and call into question the apparent "fads" in treatment of LCIS (i.e., the swing from treating all/most cases with preventive bilateral mastectomy during the 1940's--1960's to the "watch and wait" option favored with the advent of low-dose mammography beginning in the 1970's). Perhaps of even greater importance, however, is the finding that long-term, prospective data through 1995 documenting the clinical course of LCIS raises crucial questions

about and challenges to the classic studies previously published using much earlier data, i.e. from the 1930's through the mid 1970's.

II. Development of the Decision Model

A. Basic Decision Analysis Concepts

Decision analysis is one of a number of informatics methods that can be helpful for making therapeutic and diagnostic decisions which involve complex trade-offs (Weinstein & Fineberg, 1980; Kassirer & Kopelman, 1991). Typically, trade-offs in medical decisions mean that the therapeutic or diagnostic modalities which are most effective also tend to be the most risky, most uncomfortable, most expensive, or otherwise undesirable. The benefits of the most efficacious modalities must be weighed against their risks, costs, or quality of life decrements in determining which course of medical action is preferred. Where there are no trade-offs, e.g., when the most efficacious therapy is also the least invasive and least risky, decision analysis is unnecessary to arrive at the optimal course of action. The use of decision analysis becomes more obvious as decisions become more complex. Applications of decision analysis have a relatively long history in the medical literature on prevention of tuberculosis (See Jordan et al., 1991a; Jordan et al., 1991b), and have recently begun to appear in the breast cancer literature. (See Hillner et al., 1996.)

⁴To perform decision analysis, the following tasks must be performed:

1. A decision tree must be developed which incorporates all relevant clinical options, as well as all possible outcomes associated with each option. A decision tree is "read" from left to right, from point of entry, through decision options, followed by outcomes.

2. Each outcome included in a decision tree must be associated with a probability that it will occur. These probabilities are typically derived from existing literature, but may also be derived from existing databases or the estimates of qualified experts. It is typical for probabilities in a decision tree, typically called "parameter estimates" to be drawn from a number of diverse sources, each of which provides a "best estimate" for the parameter in question.
3. Each final point on a decision tree must be associated with a utility value, an indicator of desirability. Values may take the form of life expectancies, quality adjusted life expectancies, values alone, costs, or a combination of the above. Assignment of utility values is often the most subjective, and perhaps weakest link in many decision trees.
5. When all of the above pieces are set in place, a full decision model has been developed. To analyze the model, a process known as "averaging out and folding back" is performed. This process consists of analyzing the model from left to right (the opposite of how it is initially read), and consists of multiplying utility values against immediately adjacent probabilities, adding together the sums of these products for all branches following one node, then continuing to multiply that result against the next adjacent probabilities. What results is one number associated with each clinical option presented in the model. If numbers such as life years are used as utilities, the final results for each option will be expressed in life years. If costs are used, the final results for each option will be expressed in cost figures. There are no statistical tests for determining whether the results of a decision analysis are statistically significant: One selects the option which maximizes life expectancy or high quality life expectancy, or which minimizes cost.

B. Specific Decision Models Projected for Use in this Project

Figures 1 and 2 illustrate the decision trees initially considered for use in this project. The difference between the two trees is that the first tree specifies time frames within which the full model would be analyzed, while the second tree includes a Markov node which permits the iteration of probabilities over a selected time span (e.g., every year, every five years, every ten years) thus allowing a more detailed inclusion of conditional probabilities which may change over time (e.g., as when risks of invasive cancer increase with specified increments in age). Both kinds of models can be useful: The first is more applicable in situations characterized by “flat” risk curves, i.e., constant risks per time intervals of interest in the study. The second is helpful when conditional probabilities change over time.

These models which guided the search for parameter estimates and utility values were evaluated by the clinical oncologist who served as subspecialty consultant on this project, Robert L. De Jager, M.D., F.A.C.P., who is currently on the faculty of the U.T. M.D. Anderson Cancer Center in Houston.

The models were programmed by Richard L. Montgomery, D.D.S., M. P.H. using the decision analysis shell program, *TreeAge*, which became available during the first year of this project and which permits traditional decision modeling as well as Markov chaining and excellent graphic representations both on computer and hard copy. All programming was initially performed on 486 personal computers, with the later use of pentium processor machines to manage more effectively the large data sets which required manipulation and analysis of information to fine-tune parameter estimates.

As can be seen in Figures 1 and 2, decision models were initially intended to include not only preventive bilateral mastectomy and a no surgery (“watch and wait” with intensive screening)

option, but also to separate surgeries with and without reconstruction. While there was no expectation that life expectancies would change on the basis of reconstruction or not, it was anticipated that quality of life adjustments would differ significantly for these options. Later empirical data suggested the contrary: That no significant differences in quality of life adjustments were obtained for surgery with and without reconstruction. Consequently, the decision models which were analyzed and are discussed in Section V have omitted this distinction.

Finally, the project had been planned to analyze decision models for women of varying ages. However, data analyzed during the course of this project limited decision models to women aged 45 and younger, based on the finding (discussed in detail under Section III) that risk curves for older women did not warrant consideration of whether to perform preventive bilateral mastectomies.

C. Software Products Produced in this Project

Presently, the decision models produced in this project are capable of being run on 486 DOS-based personal computers. The models are capable of being tailored to specific women's combinations of risk factors and personal utility values. However, new research on molecular genetics, availability of antiestrogens for primary prevention in high risk women, and changes in surgical procedures for lymph node dissection suggest that additional work be undertaken to elaborate the existing models to incorporate these features. Such directions are discussed more fully in Section VI of this report. Drs. Jordan (P.I. on this project) and De Jager are continuing to collaborate with these issues in mind, as well as to seek corroboration of the parameter estimates found herein by examining a data set available at U.T. M.D. Anderson Cancer Center.

Jordan, Montgomery, Dubois, and De Jager (1996) were invited to present some of these further directions at the International Lymphology Symposium in Brussels, Belgium; and have submitted an abstract exploring some of these issues to the American Association of Clinical Oncology for consideration for the 1997 meeting. Results of this investigation have been submitted in preliminary abstract form for the DOD meeting "Era of Hope" to be held fall, 1997. (A more detailed listing of presentations and publications is included in Appendix A.) Finally, Dr. Jordan submitted a follow-up IDEA grant to support continuing efforts on this project, and is awaiting determination regarding the application.

III. Derivation of Parameter Estimates

A. Characteristics of Existing Databases and Pivotal Investigations

This research project was designed to explore relevant, existing databases, as well as previous studies of risks associated with LCIS, in order to obtain optimal parameter estimates and parameter ranges for the decision models which would be developed. Evaluation of the available resources began during the first year of the project, and continued throughout the second year, as new data became available. Additional work was completed during several months following the termination of funding, because information about additional cases of invasive cancer (IC) diagnosed in 1995, following an earlier diagnosis of LCIS, became available.

To derive risk estimates for the decision models, this project evaluated the following registries and investigations, which are discussed critically below:

1. The Surveillance, Epidemiology and End Results (SEER) Program
2. The Connecticut Tumor Registry (State of Connecticut Department of Health)

3. Four classic, retrospective studies aimed at deriving estimates of LCIS-associated risk of invasive cancer
4. The Danish Breast Cancer Cooperative Group (DBCG) Registry.

SEER

In 1971, the National Cancer Act mandated the establishment of the National Cancer Program under which the SEER Program was developed. This database focuses on incidence and mortality rates associated with a broad range of cancers, including breast cancer, occurring in subgroups of the U.S. population. Data are obtained from a number of sources, including individual State cancer registries. Nine geographic areas comprise the present SEER database: Connecticut, Iowa, New Mexico, Utah, Hawaii, Detroit, San Francisco, Seattle-Puget Sound, and Atlanta. Breast cancer data may be analyzed for the entire SEER database, or by specific registry/geographic area.

During the first several months of this project, i.e., summer and fall of 1994, the existing SEER database (at that time available on tape) was ordered and mounted for use on a VAX/VMS system at New York University's Academic Computing Facility. The data contained in this tape comprised cancers first diagnosed within the 1973--1977 time period. (Since the time when this data tape was obtained, SEER data in updated versions have become available through a number of other vehicles, including a National Institutes of Health World Wide Web Site, which permits on-line querying using microcomputers.)

While some specific registries contributing to SEER contain additional information, the overall SEER database was not designed with longitudinal data as a primary focus. Consequently, the

structure of this database tends to obscure trends in individuals over time, i.e., risks of LCIS eventually showing as Invasive Cancers.

The initial step in obtaining overall SEER data relevant to this project consisted of separating cases designated as *in situ* histologic behavior from cases designated as malignancy. This variable is entered dichotomously in the SEER database; and it follows that grade of malignancy is provided solely for those cases with malignant histologic behavior. The absence of grading for virtually all *in situ* cases extracted from the SEER database served as a validity check on the cases needed for this investigation. The "punch" for *in situ* histologic behavior in SEER can include both LCIS and DCIS, as well as a combination of both.

Unfortunately for the purposes of this project, while the SEER database is designed to use unique identifiers for each individual patient, cases are not automatically linked over time. That is, if a case is recorded initially as LCIS, designation non-malignant, and reenters a registry later as an invasive cancer, this second entry is not automatically added to the first. Attempts are made to preserve the unique case number assigned to each patient, though this does not always occur (see below). In other words, each entry in the SEER database represents an incident cancer, which may or may not replicate a given patient (who may be entered more than once). This structure is understandable given the goals of SEER, which are primarily epidemiological rather than longitudinal in a strict sense.

From our initial work on the SEER database during the project's first year, 48,000 cases of malignant breast cancers were separated from 2,426 cases of *in situ* findings, all diagnosed in the 1973--1977 timeframe. When the *in situ* cases were examined in detail, it was found that a number of cases had been inappropriately duplicated in the data entry, i.e. the same individual was

identified with more than one “unique” identifier. There appeared to be a variety of reasons for this duplication; for instance, if a respondent’s marital status changed over the course of the study, the respondent might be entered as two different people. A total of 37 “duplicate” cases were identified through our creation of a variable to track inappropriate duplication; and a resulting sample of 2,331 cases was used in further analyses.

Unfortunately, the overall SEER database contained no readily usable mechanism for tracking the clinical course of women diagnosed with LCIS, e.g., data regarding later cancers, mortality/survival either subsequent to diagnosis or to diagnosis and treatment. We explored the feasibility of attempting to extract only LCIS cases, and linking the extracted LCIS database with later, matching entries which would provide follow-up data, but were unsuccessful. There were two major reasons for this difficulty: first, the size of the total database made manipulation extremely difficult at the time; and second, considerable differences appeared to exist in the ways in which diagnoses of *in situ* were derived (thus, making us wary of moving forward with attempts at linking entries.)

In lieu of using overall SEER data to establish parameter estimates for decision models, descriptive data regarding *in situ* cases were extracted to serve as basis against which to evaluate data from other registries.

Descriptive data obtained from the 2,331 *in situ* SEER cases indicated the following:

1. Mean age of women with this diagnosis was 55.70 years, with a standard deviation of 13.21 years. Median age was 51 years.
2. Reporting source was overwhelmingly hospital, accounting for 2300 of the 2331 cases.
3. The overwhelming proportion of cases were in Caucasian women (N=1891),

with 129 reported as Caucasian-Hispanic, and 124 as African American.

4. The majority of women were married (N=1599), an additional 368 widowed, 150 never married, and 140 divorced.
5. Site of finding varied. (Given new data suggesting that site and diffuseness of lesions might assist prediction of later invasive disease (Ottesen, et al., 1993), this information could be of interest.)

More complete breakdowns of the 2331 SEER cases may be found in Appendix B.

The Connecticut Tumor Registry

As noted above, the State of Connecticut has been a contributing registry to SEER since its inception. However, the Connecticut Tumor Registry has a much longer history than SEER, since it was initiated shortly after Foote and Stewart (1941) identified LCIS as a unique lesion. The primary reason for this early initiation of a registry in Connecticut was a suspicion that LCIS was being found in uncommonly high frequencies in that State. Thus, a tumor registry was set up to monitor incidence of LCIS, and also to follow LCIS cases on a longitudinal basis in order to assess risk and time to invasive disease. Surveillance procedures in this registry are excellent; cases are lost to follow-up literally only when women move out of state.

Due to the superb reputation of the Connecticut Tumor Registry, numerous investigators have used these data to generate estimates of relative risk for a variety of kinds of cancer. (Studies which have previously employed the Registry data to investigate LCIS are discussed below.)

The Connecticut Tumor Registry provided this project with 830 cases of women initially diagnosed with LCIS and otherwise benign findings, spanning the years 1973-1994. Additional

cases of LCIS which emerged at invasive cancers (IC) in 1995 were provided to this project during the fall/winter of 1996. This data set begins at approximately the time when low-dose mammography became available, and so contains cases in which "watch and wait" with intensive screening provided an alternative to preventive bilateral mastectomy.

The Connecticut Registry is designed to pay particularly close attention to cases of LCIS. With the close supervision of the Tumor Registry's Director, as well as its primary programmer, this project obtained a "clean" database of cases in which LCIS was the only diagnostic finding, i.e., there was no confounding with DCIS or other coexisting conditions. Furthermore, unless women who enter the database relocate out of State, all follow-up cancer-related data are reportable to the Registry. According to the registry's director, Connecticut has experienced one of the lowest relocation rates in the country, so this confounding variable is likely to be less problematic than it has been for other databases. Consequently, considerable faith can be placed on the Connecticut Registry as a source of prospective, longitudinal data on the clinical course of women with LCIS. On the other hand, an important caveat remains: While it is probably the oldest and best database of its kind, the CT Registry was initiated in response to extremely high rates of LCIS found in that State. Consequently, there will remain questions about its generalizability until adequate comparisons are made at other sites.

The mean and median ages of the 830 women in our CT Registry file were 53 and 50 years, respectively. Median year of diagnosis of LCIS was 1987. Of these 830 cases, 96% were Caucasian. Full distributions for this data set are provided in Appendix C.

While these 830 cases were computerized by the Connecticut Department of Health to conform to SEER format, they also contained “flags” which indicated whether they were linked to follow-up case information indicating the development or lack of development of invasive disease. When the flagged cases were separated from the others, a total of 41 cases of IC were identified between 1973 and 1995.

For women with LCIS who developed IC, the mean age of LCIS diagnosis was 57.73 years, with a median of 57 years. The mean age of IC diagnosis was 63.73 years with a median of 63.0 years. Mean follow-up time was 6.02 years with a median of 5.0 years..

Since this data set served as the primary basis for derivation of crucial parameter estimates in this project, our analyses of the data are discussed in greater detail under the section entitled “Selection of Parameter Estimates for Inclusion in the Final Decision Model.”

Four Classic Studies of LCIS and Invasive Cancer

Four retrospective studies of the risk of invasive cancer in women with LCIS are repeatedly cited in textbooks on breast diseases and clinical oncology (e.g., Harris, et al., 1992; Donegan & Spratt, 1995; Abeloff, et al., 1992), as well as in current journal articles (e.g., Ottesen, et al., 1993). Basic findings from these studies, as well as a review of critical weaknesses, follow:

1.) In a review of biopsy files from Columbia University’s College of Physicians and Surgeons, Haagensen (1986) identified 5000 patients who underwent a breast biopsy between 1930 and 1977 and who were classified as having benign disease. Haagensen reports a finding of LCIS in 297 of these cases. Of these, 10 patients were diagnosed with LCIS after a finding of

invasive disease. Fifty three, or 18% of the remaining 287 cases, developed invasive disease during a mean follow-up time of 16.3 years. At initial diagnosis of LCIS, the vast majority of women in this data set (88%) were premenopausal. Approximately half of the invasive cancers which developed occurred in the contralateral breast, and the other half in the ipsilateral breast. This last finding lends some credence to the notion that LCIS might act as a marker for breast cancer rather than a precursor lesion. Haagensen's (1986) data suggest a relatively "flat" risk curve for women with LCIS: It is estimated at approximately 1% per year (Donegan & Spratt, 1995). In related work, Haagensen et al. (1981) computed relative risks associated with LCIS using the State of Connecticut Tumor Registry incidence rates for breast cancer to generate observed/expected rates for his cases. Haagensen et al. (1981) also used this Registry to compute different relative risks for LCIS alone versus LCIS plus positive family history of breast cancer. For all LCIS cases, observed/expected case ratio was reported as 6.9:1. For LCIS without positive family history, the ratio was 5.7:1, while it rose to 8.5:1 with a positive family history.

Haagensen's (1986) work is strong in its comprehensiveness and length of follow-up, and in its low number of lost cases (N=2). However, the series ends with data collected in 1977. His earlier work (Haagensen et al., 1978) ended with 211 cases of LCIS by 1972. Consequently, an additional 86 cases were included in the later report, and covered an additional five years of data. This cohort of cases cannot possibly represent the women who presently undergo breast biopsies, nor is it representative of cases evaluated after the advent of low-dose mammography in the mid 1970's. In reviewing Haagensen's findings (1986), one might ask what kind of bias might exist in a sample of women undergoing breast biopsies before an awareness of high breast cancer risk in the U.S. became common, and before a safe screening technology became available? Might this

sample reflect a population at higher risk for breast disease than the “normal” population of its time?

2.) The Memorial Hospital series (Rosen, et al., 1978), also retrospective, was comprised of 99 patients, fifteen cases lost to follow-up, and a mean length of follow-up of 24 years. In this series, 78% of the women were aged 50 or less at time of diagnosis of LCIS. Consistent with Haagensen’s (1986) report, this series showed that more than half of the patients with LCIS who developed invasive cancer developed it in the contralateral breast. This series also consists of data which may be too old to adequately represent current cohorts of women with LCIS. Inconsistent with Haggensen (1986), Rosen et al.’s (1978) report showed an extremely high risk of 37% associated with LCIS. This risk was found to increase with increasing length of follow-up and increasing age. Like Haagensen (1986) Rosen et al. (1978) used the Connecticut Tumor Registry to calculate relative risks of developing invasive cancer given LCIS, and reported a risk ratio of 9:1.

This series may also be criticized for the high percentage of patients lost to follow-up, particularly given the fact that patients who develop disease are more likely to be “found” than are patients who remain disease-free. Kinne (1992) noted that if the 37% risk were corrected for attrition, the risk would fall to 31%. He attributes the fact that this risk remains high to the long follow-up period, since in the Rosen et al. (1978) report more than half the patients who developed invasive cancer did so more than fifteen years after the initial biopsy. In evaluating time to invasive cancer, it is critical to bear in mind what is meant by this terminology in a given report, and at specific points in time: In particular, one must bear in mind that prior to mass screening with mammography, and little education regarding breast health, invasive disease was

more likely to be found at later stages, with the passage of more time and greater possible *lead time bias*. Consequently, the Rosen et al. (1978) series does not appear useful in projecting current risks or time to onset of invasive cancer.

3.) A smaller retrospective series consisting of 35 patients with none lost to follow-up was performed by Wheeler et al. (1974), again on a dated sample. Women in this series were aged 33 to 49 years. During a mean follow-up of 15.7 years, six patients, or 17.1% developed invasive cancer. Five of these six patients developed their cancers in the contralateral breast.

Given the fact that this series was retrospective, as well as consisting of a small sample, it is difficult to have confidence in the percentages or risk ratios that were derived.

4.) In a Scandinavian sample, Andersen (1974) retrospectively studied 3299 benign lesions, and found 52 cases of LCIS with none lost to follow-up, and a mean length of follow-up of 15 years. Again, the women diagnosed with LCIS were primarily premenopausal. The series showed a 28.8% risk of invasive disease associated with LCIS; with invasive cancers occurring half in the ipsilateral breast and half in the contralateral breast. In this series, the highest risk of invasive cancer occurred in the first one to five years after biopsy, with later decrease.

As in the other three series discussed above, this sample is dated, and may be unlikely to reflect risks presently applicable to women diagnosed with LCIS.

There are some striking similarities as well as differences across the above studies. The similarities are as follows:

--In all four studies, women were primarily premenopausal at time of diagnosis of LCIS.

However, it is important to note, as per Kinne (1992), that the overwhelming majority of benign

lesions that require biopsy appear during the reproductive years, and given that LCIS is an incidental finding on biopsies done for other purposes, this age distribution is not surprising. Kinne further notes that the risk of invasive cancer does not decrease with menopause, as might be inferred from the above data.

--All studies reported increased risk of invasive cancer associated with LCIS, but did so retrospectively. Thus, the conditional probability of getting invasive cancer given LCIS (i.e., predictive value) is difficult to assess in all four series.

--All studies reported at least equal risk of invasive cancer in the contralateral breast, thus lending support to the argument that LCIS is not a precursor lesion. (Of course, these studies did not contain data on mirror-image biopsies of the contralateral breast to yield information regarding possible LCIS in both breasts.)

In addition to the use of different data sets, differences in the studies include the following:

--Time to invasive disease was found to be quite different in three of the four series: Haagensen's data lent support to a relatively flat yearly risk after diagnosis of LCIS; Rosen et al.'s data suggested that risk increases over time and with increasing age; and Andersen's data supported highest risk in the first five years after a finding of LCIS.

--While all four studies reported an increased risk of invasive disease given a finding of LCIS, the risks estimates were dramatically different, ranging from a low of 18% to a high of 37%, a difference of more than 100%.

Danish Breast Cancer Cooperative Group Prospective Trial

Ottesen et al. (1993) have extracted short-term findings regarding LCIS from the Danish nationwide prospective trial. This study comprised 69 patients diagnosed with LCIS from 1982 through 1987, with a median follow-up of 61 months. The authors reported a median age of 47 years, but this included women with DCIS as well as those with LCIS. For cases of pure LCIS in the presence of otherwise benign findings, the incidence rate of invasive cancer was compared with the incidence rate of an age-matched Danish population included in the Danish Cancer Registry for the same period of time. Results showed an 11 fold increase in risk, corresponding to a recurrence rate of 17%.

The authors noted that their risk rate of invasive cancer was high given the short-term nature of the study. They attributed this high risk in part to a prospective design, which included close surveillance of patients, enabling them to make diagnoses early. They also noted, however, that all cases of invasive cancer were palpable at time of diagnosis, two of which already showed axillary lymph node involvement, and only two of which were visible on mammography. This disappointing finding was attributed to the ages of the women at time of diagnosis of invasive disease: between 35 and 52 years old when abundant glandular tissue which is frequently characterized by fibrocystic changes makes mammography less useful than later in life.

The different design of this study as well as the time during which the patients were enrolled makes comparisons between its findings and the older, retrospective studies virtually impossible to make. One possible, alternate explanation for the high rate of invasive cancers found during the short period of time in the Danish study might be that prevalent cancers are being caught during the early part of the series, and that if the study were to continue for time frames comparable to the retrospective studies critiqued above, the risk rates might be quite different.

N.B. When the present investigation was proposed, it had appeared that the Swedish Cancer Registry would be useful to this project. However, when the Swedish data were accessed, we found no way to investigate longitudinal trends. The Danish Registry data were then used as an alternate source.

B. Selection of Parameter Estimates for Inclusion in the Decision Model

One of the most difficult tasks in developing a decision model is selecting the best parameter estimates for each branch in the decision tree. The most critical parameters to estimate for this project were: the risk of developing invasive cancer given a diagnosis of LCIS, and the time to development of invasive cancer, i.e. a risk curve. Other essential estimates, such as survival rates for early stage breast cancer have been investigated more extensively and are based on more solid empirical foundations. Similarly, surgical mortality as an anesthesia related risk has been well-documented.

LCIS specific parameter estimates

In the search for best estimates of the risk of invasive cancer currently confronting premenopausal women diagnosed with LCIS, as well as the risk curve, results of the retrospective studies critiqued above were judged to be inadequate. The reason for this was primarily the fact that data included in these studies continued only up through the mid 1970's at best. In the age of high awareness of breast cancer risks as well as the current availability of low-dose mammography, these earlier data appear to be anachronistic.

The estimates sought for inclusion in this study were lifetime risks and risks projected over specific ranges of time. Such projected time-specific risks are more useful in counseling women regarding breast health (as per Donegan & Spratt, 1995) than are relative risks. They are also the estimates necessary for calculating expected values in decision models.

In contrast to data used in the studies discussed above, data available to this project from the Connecticut Tumor Registry consisted of cases spanning the years 1973 through 1995, a twenty-three year time frame. The reputation of this Registry is superb, as attested to by the attempts of other researchers to use it to generate relative risks. Furthermore, the timeframe of the data is both relevant in terms of being within the advent of low-dose mammography and comprising long term follow-up. Consequently, these data avoided the pitfalls of being anachronistic as well as of being biased by skimming prevalent cancers as might occur in a short-term series. The major caveat in using the Connecticut Registry is the initial reason for its inception: particularly high rates of LCIS in the State of Connecticut. However, the present project was not designed to study incidence or prevalence rates of LCIS, but rather to investigate the behavior of LCIS in women diagnosed with this finding. There was no reason to believe that LCIS diagnosed in Connecticut would behave differently from LCIS diagnosed elsewhere, despite possibly higher rates of occurrence.

As noted in the previous section, the CT Registry provided this investigation a total of 830 patients diagnosed with LCIS and otherwise benign findings, between the years 1973--1995. The Director of the CT Registry provided the follow-up linkages in the data set, providing this project with 41 cases of the initial 830 which had been subsequently diagnosed as invasive cancer. These 41 cases comprised 4.9% of the LCIS CT Registry population. Consequently, the risk of

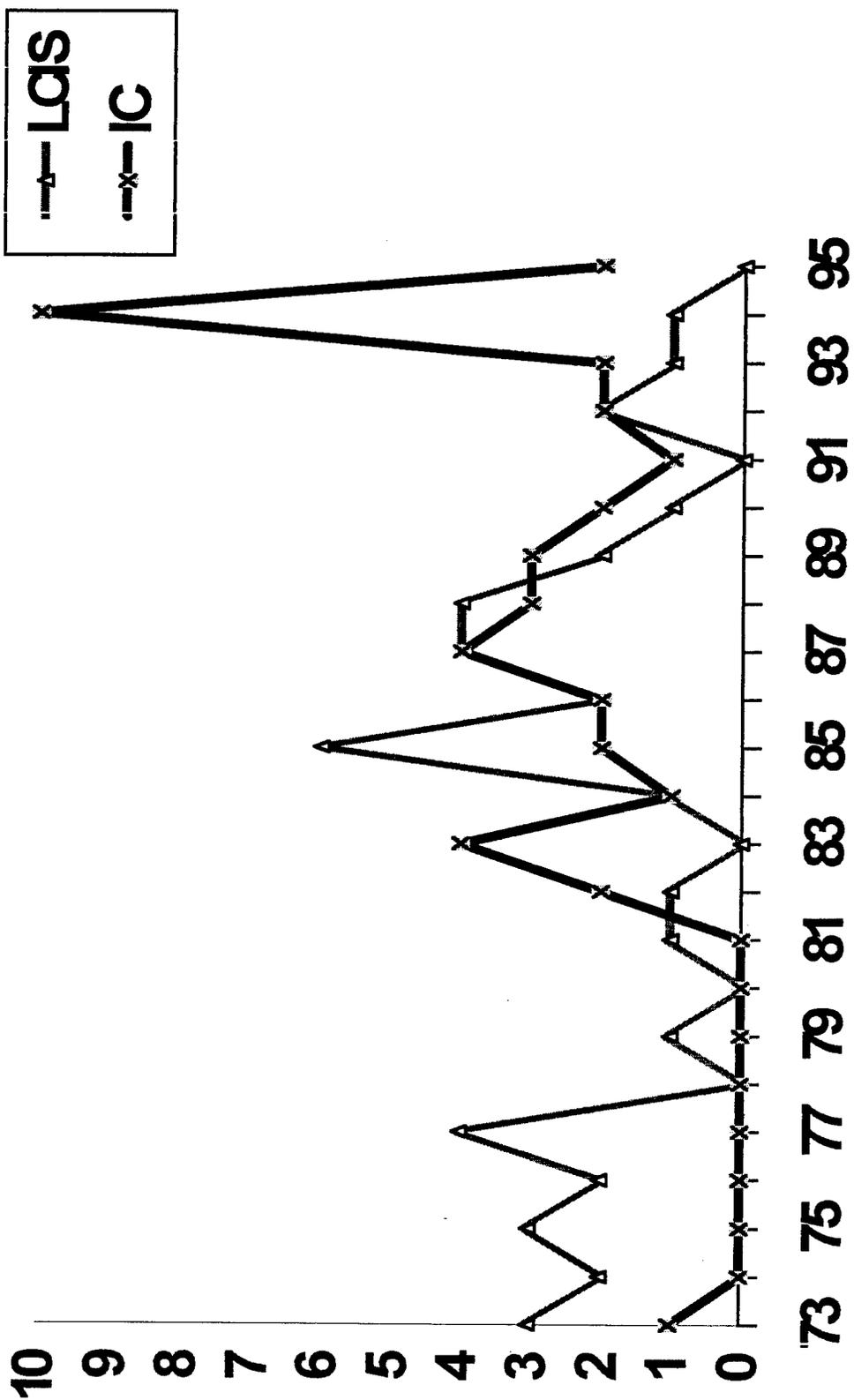
developing invasive cancer given a diagnosis of LCIS in this data set was 4.9% within an average of 6.02 years.

Compared with results of the earlier, retrospective studies of LCIS, this rate of invasive cancer was extremely low. The correctness of the data sets was double checked with the Registry Director as well as the programmer at the Registry. { Relocation out of State was considered as a confounding variable; but relocation was found to be extremely low in Connecticut.) Additionally, time to invasive cancer was relative fast, thereby minimizing the effects of attrition. (This is discussed in detail below.) Finally, there was no reason to hypothesize *differential attrition*, i.e., that the rate of relocation would be significantly different for women with LCIS who developed invasive cancer than for women who did not. Consequently, relocation was not seen as a potent threat to the validity of the data. Descriptive statistics for the LCIS cases who developed invasive cancer are shown in Table 1.

Table 1. Means, Medians and Standard Deviations for Age and Time Variables for Women with Invasive Cancer			
Variable (YEARS)	Mean	Median	Standard Deviation
Age at Dx of LCIS	57.73	56.5	11.27
Age at Dx of IC	63.73	62.5	10.31
Time to Dx of IC	6.02	4.5	5.47

Trends in numbers of cases of LCIS and IC diagnosed per year are illustrated in Figure 3.

FIGURE 3
Trends in Numbers of Cases of LCIS and IC
Diagnosed per Year



Data from the CT Registry indicated that risk for invasive cancer was greatest in the first five years following diagnosis of LCIS, thus in agreement with Andersen's (1974) findings. The breakdown of the 4.9% risk was as follows (Table II):

Table II. Risks of IC by Five Year Intervals			
Within first 4 years	25 cases	61 %	Corresponding Risk 2.99 %
6 - 10 years	8 cases	20 %	.98 %
11 - 15 years	5 cases	12 %	.59 %
16 years or more	3 cases	7 %	.34 %

Data from the National Cancer Institute Surveillance Program extracted by the Susan B. Komen Breast Cancer Foundation (1996) provides a current breakdown of breast cancer risks by age, throughout the lifespan. (See Table III.) Reflecting new data included in NCI statistics, the risk estimates are projected through age 85, irrespective of actual life expectancies of women born in specific years, of specific ethnic groups, etc. These data are overall estimates, and do not focus separately on women at particularly high or low risk for breast cancer.

Table III. Overall Risks of Breast Cancer for American Women, 1996

AGE:	Risk expressed as fraction	Risk expressed as Cumulative %
25	1/19,608	0.0000509
30	1/2,525	0.000396
35	1/622	0.0016077
40	1/217	0.0046084
45	1/93	0.0107526
50	1/50	0.02
55	1/33	0.03
60	1/24	0.04
65	1/17	0.058
70	1/14	0.07
75	1/11	0.09
80	1/10	0.10
85	1/9	0.11

Source: NCI Surveillance Program

Risks of invasive cancer for women with LCIS derived from the CT Registry were compared with risks projected by age in the NCI data. Comparisons of risks for women diagnosed with LCIS versus the normative population are shown for ages 40 and 45 in Tables IVa and IVb below. The risks of invasive cancer given a diagnosis of LCIS are not considered to be age-specific, but rather a function of time from identification of LCIS. When these risks are mapped against a normative risk curve, LCIS appears to pose increased risk of invasive cancer only for women aged 45 and younger. For women over age 45, LCIS does not appear to pose a heightened threat of invasive cancer. Furthermore, by age 50, the risks given LCIS begin to

reflect almost exactly the risks experienced by the general population, as indicated in Table V. In examining this last Table (for women with LCIS diagnosed at age 50), it is important to remember that a diagnosis of LCIS does not indicated a reduction in breast cancer risk post-menopause (Kinne, 1992). While the peak time for diagnosis of LCIS is typically premenopausal, the peak time for occurrence/diagnosis of invasive cancer is not. Consequently, after age 60, the risk for a woman diagnosed with LCIS at age 50 would probably revert to the risk calculated for the general population.

TABLE IVA. START AT AGE = 40		
BY AGE	WITH LCIS (CT registry estimate)	WITHOUT LCIS (NCI overall estimate)
45	2.99 %	1/93 or 1%
50	3.97 %	1/50 or 2%
55	4.56 %	1/33 or 3%

TABLE IVB. START AT AGE = 45		
BY AGE	WITH LCIS (CT registry estimate)	WITHOUT LCIS (NCI overall estimate)
50	2.99 %	1/50 or 2%
55	3.97 %	1/33 or 3%
60	4.56 %	1/24 or 4%

TABLE V. START AT AGE = 50		
BY AGE	WITH LCIS (CT registry estimate)	WITHOUT LCIS (NCI overall estimate)
55	2.99 %	1/33 or 3%
60	3.97 %	1/24 or 4%
65	4.56 %	1/17 or 5.8%

Because risk of invasive cancer given LCIS calculated in the present study was not age-specific, and because the risk of invasive cancer appeared to reflect the risk for the general population for women diagnosed with LCIS at ages 50 and higher, it appeared important to explore the relation of age at LCIS diagnosis to the time interval when IC was diagnosed. Time to diagnosis of invasive cancer was regressed on age of LCIS diagnosis, and year of LCIS diagnosis was entered in to the equation to covary possible trends over time. The correlation matrix obtained for these three variables are presented in Table VI.

Table VI. Correlation Matrix, n=41			
	Time to IC	LCIS Age	LCIS Year
Time to IC	1.000	-.415*	-.668*
LCIS Age	-.415*	1.000	.480
LCIS Year	-.668*	.480*	1.000

* $p < 0.01$

The significant negative correlation between age at LCIS diagnosis and time to diagnosis of invasive cancer indicates that the younger the woman at diagnosis of LCIS, the longer the time interval would be to occurrence/diagnosis of invasive cancer. This finding is consistent with the

notion that risks previously thought to be associated with LCIS might, in fact, represent something closer to the normal risks for women moving into the age periods associated with higher breast cancer risk. On the other hand, a woman's age at diagnosis of LCIS accounts for only about 20% of the variance in time to invasive cancer, leaving abundant room for the interplay of other factors.

The significant negative correlation between year of LCIS diagnosis and time to diagnosis of invasive cancer is not surprising, since the later the year, the less follow-up time would have been possible for diagnosing invasive disease.

Results of the Multiple Regression are summarized in Table VII. Taken together, year of LCIS diagnosis and age at LCIS diagnosis accounted for approximately 46% of the variance in time to diagnosis of invasive disease. While this is an impressive proportion of explained variance, it is attributable primarily to year of LCIS diagnosis even when the variable age at LCIS diagnosis is forced into the equation first. Consequently, these results reinforce what was seen in the correlation matrix: that a later year of LCIS diagnosis was associated with a shorter time to diagnosis of invasive disease.

Table VII. Multiple Regression Summary Table			
Multiple R	0.66845		
R Square	0.44683		
Adjusted R Square	0.43264		
Standard Error	4.12312		
	DF	Sum of Squares	Mean Square
Regression	1	535.53989	535.53989
Residual	39	663.00450	17.00012
F =	31.50213	Signif F =	0.0000

Taken together, the intercorrelations and multiple regression results suggest the following possibilities:

1. Women diagnosed with LCIS at younger ages have a longer time to diagnosis of invasive disease because what is actually being measured is the increased risk of invasive cancer for aging women. In statistical terms, this constitutes a *lead time bias* which could be inappropriately interpreted as increased risk associated with LCIS.
2. On the other hand, the fact that the relation between age at LCIS diagnosis and time to diagnosis of invasive disease is only moderate, as much as 80% of the variance in time to invasive disease might be due to factors other than lead time bias, such as the increased risk of invasive disease associated with the years immediately after LCIS diagnosis regardless of age.
3. The fact that approximately one third of the variance in time to diagnosis of invasive disease is accounted for by year of LCIS diagnosis might suggest that a few more cases of invasive disease

might have been identified in this data set if follow-up time for the later identified cases of LCIS in the total data set of 830 cases were extended. However, even if the number of cases of invasive disease were “corrected” for this proportion of variance, the increase in numbers of invasive disease cases would be only 13.7. Added to the 41 diagnosed cases of invasive disease, this “corrected” figure of 54.7 would raise the risk of invasive disease only to 6.6%--still, substantially less than the risk suggested in previous, retrospective studies (i.e., 15% to 30%).

Additional Parameter Estimates Necessary for Decision Modeling

In addition to the LCIS specific parameter estimates discussed above, estimates were required for likelihood of dying from surgery and likelihood of dying from breast cancer.

Likelihood of dying from surgery was limited to anesthesia-related causes, and set at the accepted overall rate of one person per thousand. This rate does not account for special risks, such as coexisting diseases. However, for an individual with known, coexisting risks, the decision model can readily be adjusted to accommodate increased estimates.

Likelihood of dying from breast cancer is a far more complex parameter to estimate, since it encompasses multiple issues including stage at which invasive cancer is diagnosed, therapies employed to treat the invasive cancer, efficacies of available therapies by receptor status of tumor, age of patient, and stage of disease.

To estimate likelihood of dying from invasive disease for the decision models developed in the present project, data were taken from the Early Breast Cancer Trialists' Collaborative Group (1992a, 1992b). This project represents 133 randomized trials and a total of 75,000 women, who

underwent a range of adjuvant cancer therapies (hormonal, cytotoxic, and immunologic) in addition to surgery.

The decision models developed in this project are capable of being adjusted to particular womens' specific risk characteristics. However, to illustrate the use of these models, a decision was made that in lieu of attempting to show specific trees for each combination and permutation of risk conditions possible, a decision model would be presented which captures the best estimate of average risk of dying from cancer given stage I or stage II disease. Early stage disease was selected in the anticipation that women with LCIS who do not undergo preventive bilateral mastectomy would be followed with intensive screening, as has been suggested by a number of researchers and clinicians (see Kinne, 1992). Stage of disease was not restricted to stage I based on the fact that lesions in younger women tend to be more difficult to visualize on mammography, and often are not detected until they become palpable (Ottesen et al., 1993). Since the decision trees analyzed in this project were limited to women aged 45 and younger, the caveats regarding efficacy of follow-up in younger women articulated so cogently by Ottesen and colleagues were used to help determine that this study would include stage II as well as stage I disease.

Using data presented by the Early Breast Cancer Trialists' Collaborative Group (1992a, 1992b), survival for the normal life expectancy was equated with ten-year, recurrence-free survival, at which point cure is assumed to have occurred. Combining data from a range of adjuvant therapies and Stage I and II cancers with good and poor prognoses, the best estimate derived for recurrence-free survival was 50%.

IV. Derivation of Utility Values/Quality of Life Adjustments

Two kinds of endpoints were of importance in the decision models developed for this project: life expectancies and quality of life adjustments. Life expectancies are critical since the primary argument for treating women with LCIS is to prevent early breast cancer mortalities. On the other hand, life expectancies alone are not sufficient to serve as endpoints, i.e. utility values, in the model: based on life expectancy issues alone, preventive bilateral mastectomy would be the treatment of choice for literally all women since performing the surgery virtually guarantees a zero probability of death from breast cancer. The primary argument against preventive bilateral mastectomy is not an argument based on life-expectancy but rather on quality of life. In other words, is it "worthwhile" to give up one's breasts in order to gain an assurance that one will not get breast cancer?

When decisions involve both life expectancy and quality of life issues, the optimal method of assigning utility values to endpoints in a decision model consists of incorporating life expectancies and making quality of life adjustments to those life expectancies based on more subjective aspects of the outcomes. Methods used for deriving life expectancies and quality of life adjustments are discussed below.

Life Expectancies

The most accurate projection of life expectancy is derived from census data which take into account the year in which an individual was born as well as current age, plus demographic factors such as gender and ethnicity (National Center for Health Statistics, 1993). Consequently, when solving a decision problem for a specific, individual woman at a given point in time, one would incorporate a rather precise estimate of life expectancy.

For the present project, two factors mitigated against attempting to use such precise estimates: First, while such estimates are important for decisions about particular individuals, they are not particularly helpful in illustrating a general decision model. Second, the risk curve for invasive cancer which provides a foundation against which LCIS must be viewed is projected up through age 85. While a specific woman aged 40 or 45 in 1996 might not have a life expectancy of exactly another 45 or 40 years, respectively, this is quite close to the life expectancies of 80+ years projected for women born in the 1950's and still surviving today (National Center for Health Statistics, 1993). Consequently, "normal life expectancy" was defined as 85 years for the purposes of this project.

In addition to normal life expectancies, the decision models in this project required calculation of intermediate life expectancies for final outcomes which did not result in 85 years of life. For each time period included in the decision models, a midpoint was calculated and used to provide a life expectancy. For example, if a 40 year old woman developed cancer within 5 years, a value of 2.5 was added to 40, giving an age of 42.5. If the cancer resulted in mortality, death was expected to occur within the next 10 years, yielding a midpoint of 5 years. Added to 42.5, this yielded a total of 47.5 years--an additional 7.5 years of life. This method of calculating midpoints of time intervals has been used extensively in decision analysis research (e.g., see Jordan et al., 1991a; Jordan et al., 1991b)

Quality of Life Adjustments

During the course of this project, several approaches to obtaining measures of "subjective value" were piloted. Initially, the project had been designed to obtain these measures from two sources: Through participation of women associated with the Long Island Breast Cancer

Coalition "*1 in 9*" and from an existing database on personal relationships/intimacy in post-mastectomized women generated by Carol Hoskins at New York University.

Fairly early in the project, it became clear that the quality of life adjustments required in our decision models would not be best obtained from these sources. Working with the Long Island Breast Cancer Coalition indicated that women contacted through that group's outreach services were primarily women who had already undergone treatment for breast cancer, or women who for reasons such as familial risk were particularly concerned about breast cancer prevention. It was decided that values elicited from these groups would not be valid for the "generic" woman presented in our decision models who had received a diagnosis of LCIS with otherwise benign findings. In fact, conversations with contacts at the Long Island Breast Cancer Coalition suggested to us that values obtained from women participating in this group's outreach services were likely to overemphasize the importance of aggressive prevention, i.e., be more likely than women diagnosed with LCIS alone to place high values on preventive bilateral mastectomy.

In planning this project, Dr. Hoskins data was thought of as supplementary to the more general values to be obtained from work with the Long Island Breast Cancer Coalition. Dr. Hoskins' database focuses on the trends in stress on intimate relationships during and after treatment for breast cancer. Without more general measures of value, focusing only on impact of breast cancer on intimate relationships appeared myopic. In fact, during later phases of this investigation when our own data were collected to provide measurements of value, it became clear that most women assign values on the basis of their own and significant others' perspectives, rather than thinking in terms of domains of life experience, such as intimate relationships versus work.

Following is a summary of the measurement efforts which occurred in conjunction with this project:

Phase I

Approach: Traditional attitude assessment

Concept: General attitude toward breast cancer

Scale: Likert type items

Target sample: Contacts at LIBCC and small group of premenopausal women in
Connecticut

Responses: Anger expressed by many (comments in margins, comments to researchers);
primarily consisting of "not wanting to think about breast cancer"

Validity: Poor

Reliability: Poor

Phase II

Approach: Assessment of specific psychological traits

Concepts: Stress associated with fear of breast cancer, Coping with fear of breast cancer

Scale: Modified Guttman

Target sample: Same as above

Responses: Apparent denial by many with no disease experience; very different responses
from those with disease experience (perhaps more realistic?)

Validity: Poor

Reliability: Poor

Phase III

Approach: Clarification of values from different perspectives

Concepts: Importance of own and significant others opinions in relation to specific treatment options available for LCIS

Scale: Multi-dimensional scaling, person x treatment option

Target sample: Health care providers not involved in breast cancer treatment decisions
(Third year dental students, N=70; Psychology doctoral students, N=36)

Responses: Different for different audiences; possibly quite useful as a clinical tool for helping physicians and patients work together to clarify values

Validity: Probably good for the purpose of a clinical tool

Reliability: Not amenable to traditional reliability testing such as internal consistency; However, for both reliability and validity purposes, it is important to note that this tool succeeds in eliciting different values accross treatment options as well as accross perceived opinions of significant others

Comment: The instrument described in this phase of measurement appears to be quite promising as a values clarification tool. A copy of one version of the instrument, given to the target samples indicated above, is included in Appendix C of this report. While analyses of the data obtained from this instrument are not discussed in detail herein, they are in preparation for presentation and publication elsewhere.

Phase IV

Approach: Traditional assessment of utility values in decision analysis, using both direct measures of value and reference gambles

Concepts: No hypothetical constructs such as fear or coping; instead, simply assigning values to final outcomes included in the decision model

Scale: 0 to 1, with unlimited choices carried out as many places as a respondent desires

Target sample: 214 medical students during junior clerkship in internal medicine

Responses: Clean data set, useful for making quality of life adjustments to life expectancies

Validity: No hypothetical constructs, therefore not relevant in the same way as for traditional attitude assessment

Reliability: Not amenable to traditional approaches to reliability measurement

Comment: Values obtained from this approach were incorporated into the decision models in this project.

As indicated above, the quality of life adjustments made to life expectancies in the decision models were derived from a traditional approach to eliciting utility values in medical decision making (Weinstein & Fineberg, 1980). A total of 214 medical students in their internal medicine clerkship participated in this task as part of their required week of specialty instruction in medical informatics. Students already had achieved a rudimentary knowledge of decision analysis prior to participating in this task. Responses were anonymous: No identifiers of any kind were utilized on the response sheets. Each student was given a case describing a premenopausal woman diagnosed with LCIS. After the case description, the student was requested to assigned values ranging from 0 to 1 to the final outcomes in the decision model, with two anchors provided by the researcher: 0 for immediate mortality associated with preventive surgery, and 1 assigned to no

surgery/cancer-free for normal life expectancy. Reference gamble format consisted of framing each "intermediate" outcome in terms of the best and worst outcomes given as 1 and 0.

Reference gamble format tends to provide less biased and more conservative utility values, i.e., less vulnerable to impact of extraneous variables (Weinstein & Fineberg, 1980), and may therefore be preferred over direct or "free" assignment of values. In this investigation, the reference gamble format provided values which were impacted less by the specific age and attractiveness of the woman described in the case, and were therefore utilized in the final decision models. (As with the data obtained from the multi-dimensional scaling method, these findings are in preparation for publication and have been presented at professional meetings.)

Mean utility values assigned to LCIS treatment outcomes, and used for quality of life adjustments, are shown in Table VIII below:

TABLE VIII: MEAN VALUES FOR ALL HEALTH OUTCOMES

Outcome	METHOD 1: GENERAL		METHOD 2: REFERENCE GAMBLE	
	Age < 50	Age 75+	Age < 50	Age 75+
A	.83	.83	.82	.75
B	.44	.53	.66	.70
C	.27	.38	.58	.60
D	.75	.73	.77	.70
E	.38	.47	.63	.64
F	.28	.37	.59	.62
G	GIVEN			
H	GIVEN			
I	.73	.72	.83	.74
J	GIVEN			
K	.82	.82	.88	.78
N=212				

V. Results of Decision Analyses

For final analyses, the decision model was modified to collapse surgery with and without reconstruction into the option simply labeled surgery. The reason for this modification was that no difference in life expectancies were associated with reconstruction/no reconstruction, and no

FIGURE 4

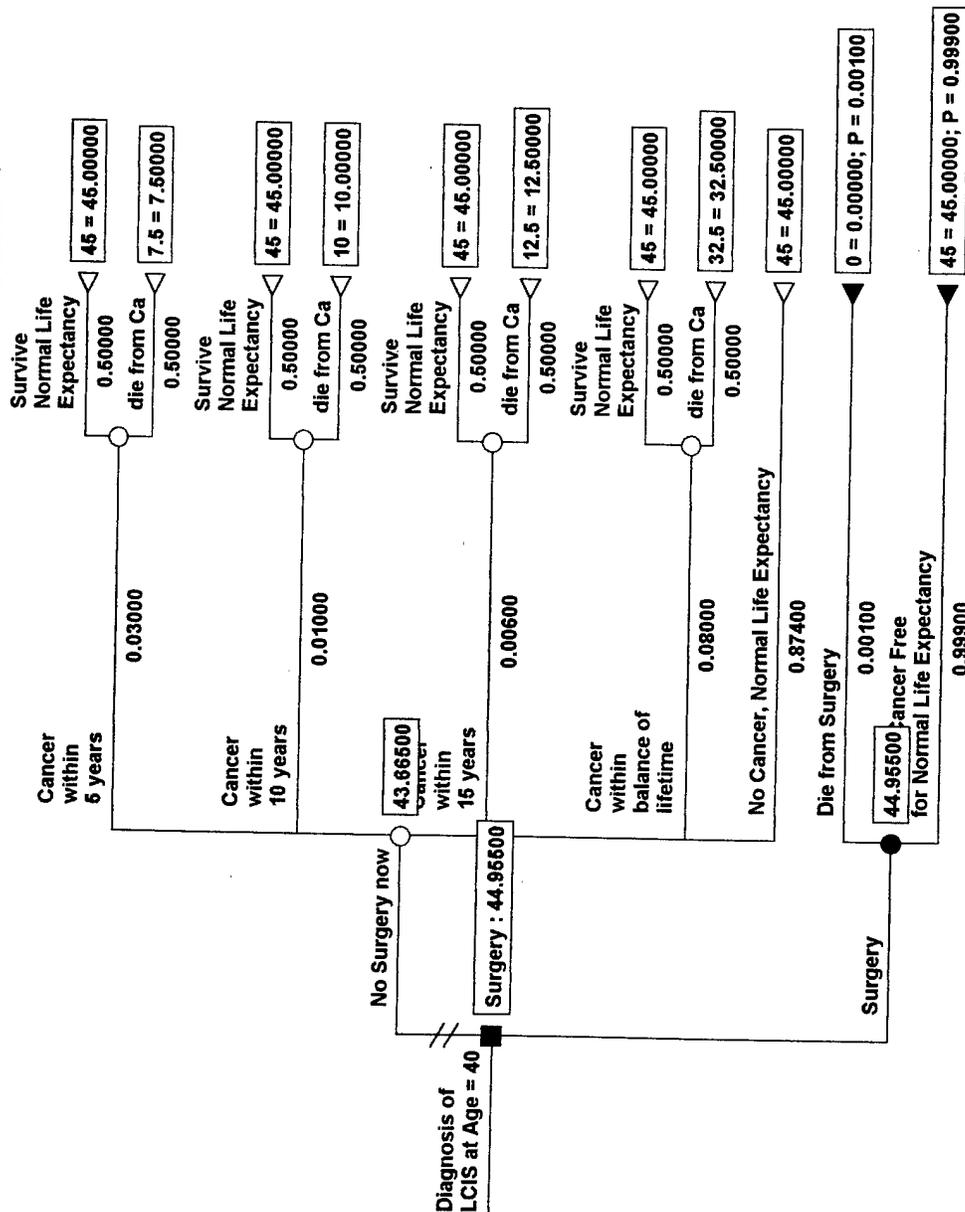
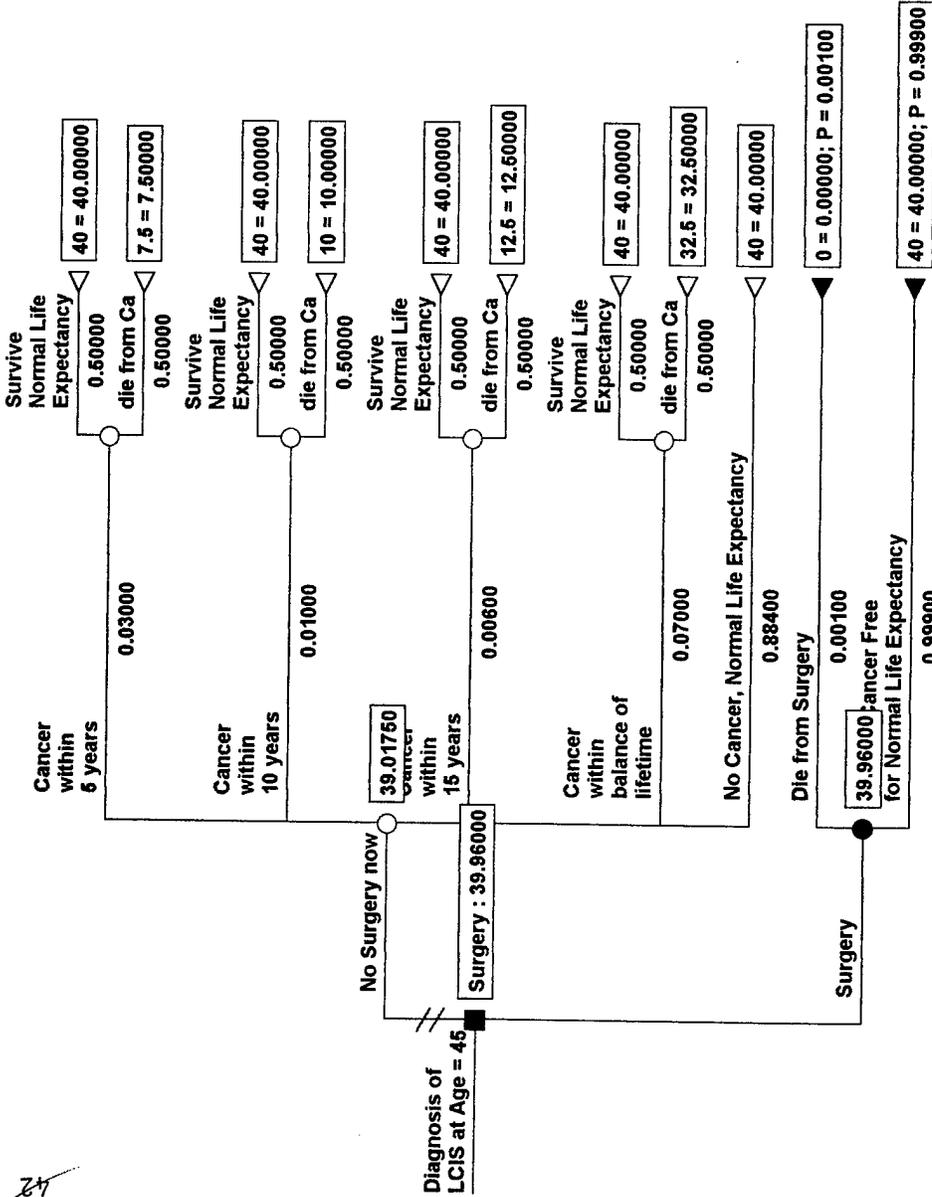
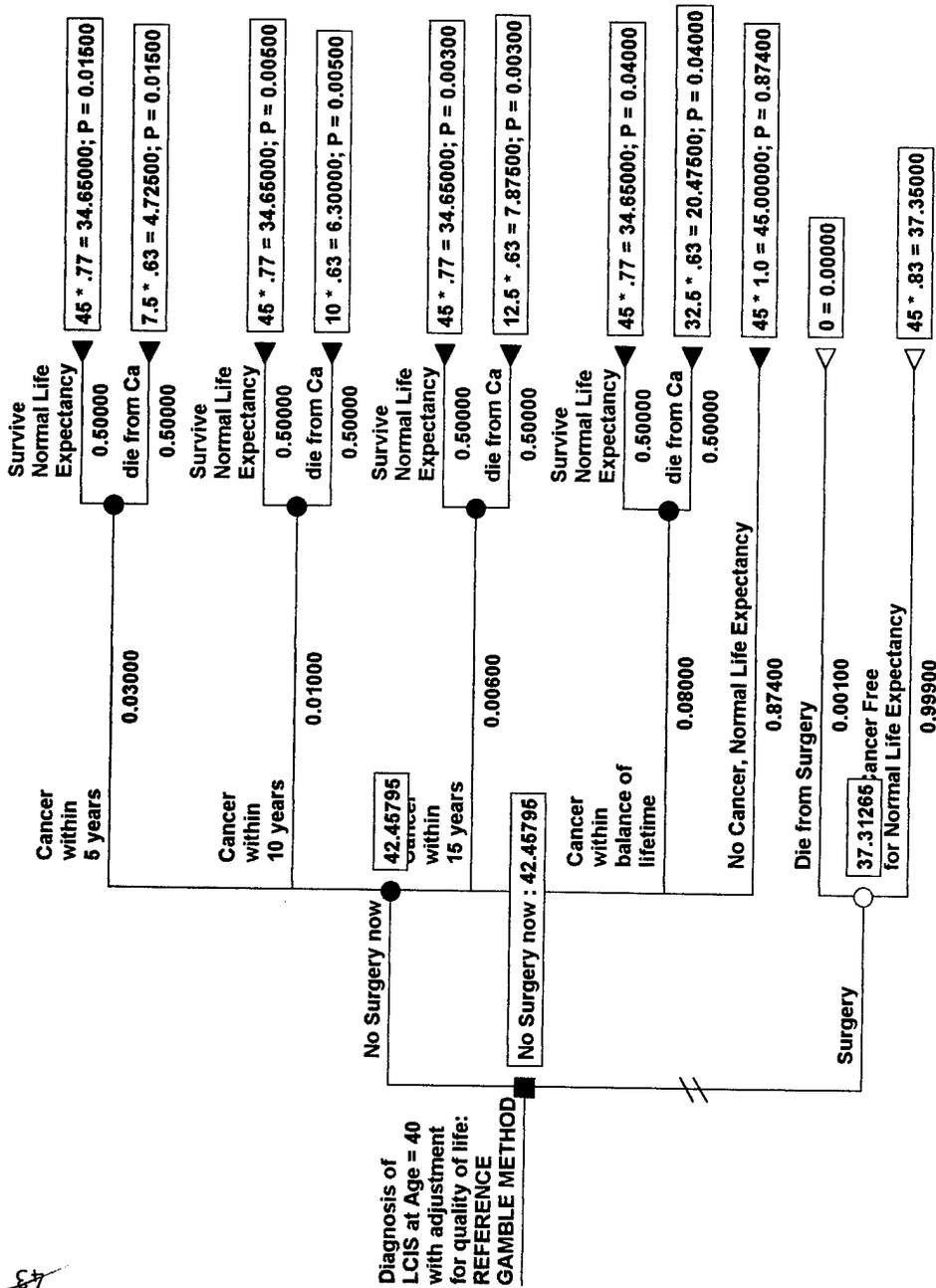


FIGURE 5



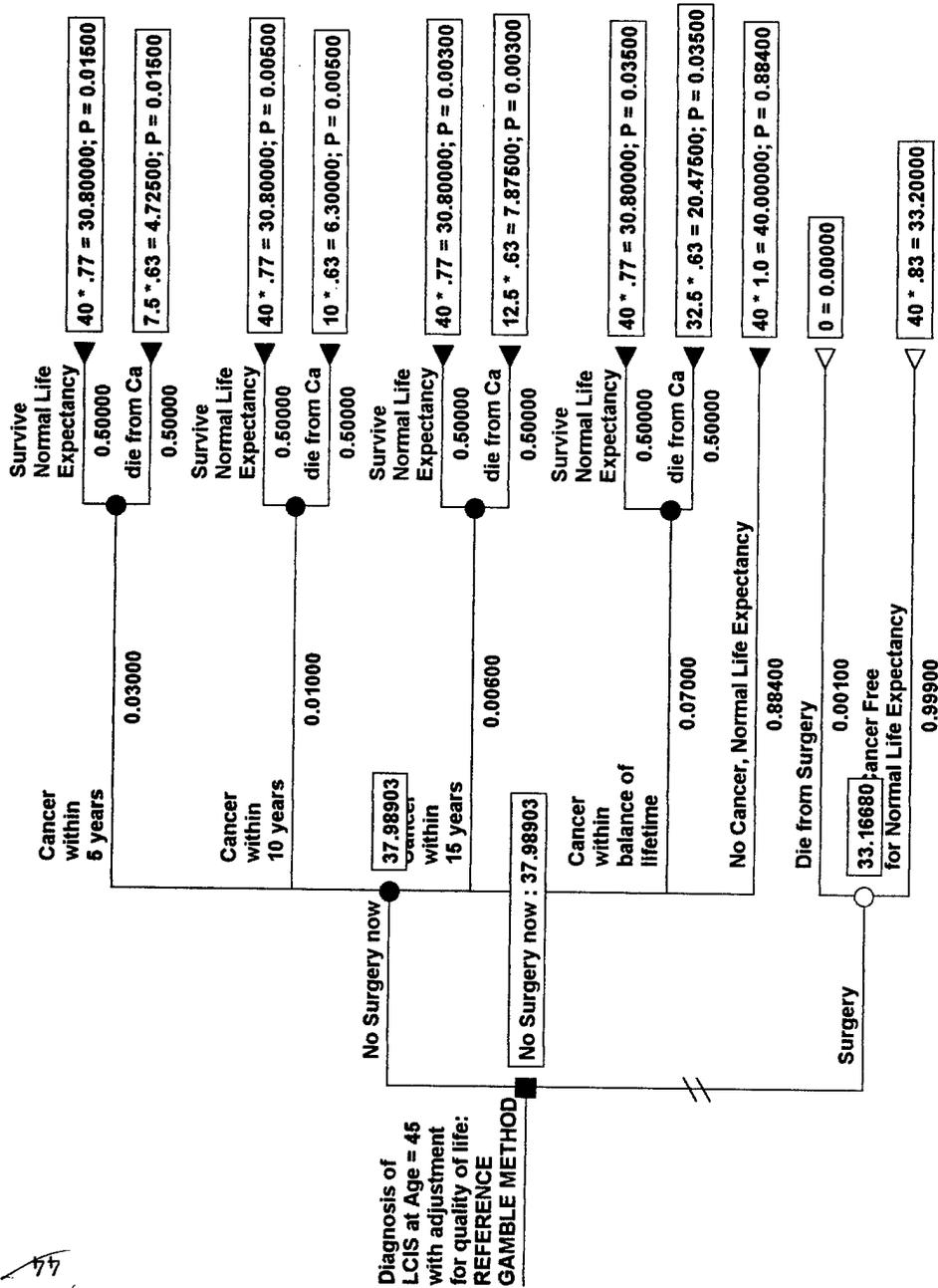
28
42

FIGURE 6



87
43

FIGURE 7



44

significant differences in utility values were found to be associated with these branches of the decision tree. The final decision models with parameter estimates, life expectancy utility values alone, and quality adjusted life expectancies, for women aged 40 and 45 are shown in Figures 4-7. In lieu of showing a Markov node, which serves as a kind of abbreviation of the conditional probabilities which follow it, conditional probabilities are shown explicitly for five time-sensitive options.

Results of the decision analyses are summarized in Table IX(a) and IX(b) below. These results may be interpreted as years of life saved or lost by following one or the other decision branch in the model. As the results indicated, when life expectancies alone were considered, the decision favored preventive surgery over intensive screening by a margin of .89 year for 40 year old women, and .94 year for 45 year old women. When conservative quality of life adjustments were made based on data from medical students, the decision favored intensive screening by margins of 5.15 years and 4.82 years for women aged 40 and 45, respectively.

TABLE IX A: LIFE EXPECTANCIES ONLY		
AGE	SURGERY	NO SURGERY/ INTENSIVE SCREENING
40	44.955*	43.665
45	39.960*	39.018

* indicates preferred outcome

TABLE IX B: QUALITY OF LIFE ADJUSTED LIFE EXPECTANCIES		
AGE	SURGERY	NO SURGERY/ INTENSIVE SCREENING
40	37.313	42.458*
45	33.167	37.989*

* Indicates preferred outcome

VI. Summary and Discussion of Findings

This project yielded two unanticipated, related findings. First, 22 years of prospective data (1973-1995) from the well-respected Connecticut Tumor Registry which were analyzed for the purposes of this project yielded much lower risks of invasive cancer associated with LCIS than had been anticipated on the basis of earlier, retrospective studies. In fact, the risks were sufficiently low that after age 45, they reflected the risks of the general population of U.S. women as expressed in National Cancer Institute surveillance data. Second, these findings made decision modeling applicable only for women 45 years and under, since decisions for women older than 45 would essentially reflect policies regarding all U.S. women. As Haagensen (1981) has suggested, since preventive bilateral mastectomy has not been promulgated for all women or even for women with familial risk factors, when LCIS risk fails to exceed risks for these other populations, there is no reason to consider preventive surgery. Decision analyses performed for women aged 40 and 45 showed that when life expectancies alone were used as endpoints, the decisions favored preventive surgery (as it would for the normative population of American women) by a margin of just under one year. When conservative quality of life adjustments were made to the life

expectancies, the decisions favored no surgery/intensive screening by margins of approximately 5 years.

A third finding, which is not quite as surprising since it has been suggested by Andersen (1974) and partially supported by Ottesen et al. (1993) is that the risk for invasive cancer in women diagnosed with LCIS and otherwise benign findings is greatest during the first five years after LCIS diagnosis, representing 61% of the total LCIS-associated risk. While there is a statistically significant, negative correlation between age at LCIS diagnosis and time to diagnosis of invasive cancer, this accounts for only about 20% shared variance. Consequently, the notion of a heightened risk after LCIS diagnosis appears to be more than an artifact of younger women waiting longer to develop cancer, i.e., more than a lead time bias.

Prior to discussing the possible meaning and implications of these summarized findings, it is important to note some limitations of the work done during this project:

1. For decision models, the assumption was made that preventive bilateral mastectomy would be 100% effective at preventing breast cancer. However, it is possible that in a very small percentage of cases, this might not be true.
2. Decision models developed in this project are capable of being fine-tuned to fit particular women's combinations of risks and values. However, the models are not generalizable to or valid for women beyond age 45 because the risks for older women were not found to deviate from risks shown for the general population.
3. The vast majority of women for whom LCIS was diagnosed, and all the women for whom invasive cancers developed, were Caucasian. This was true of the Connecticut Tumor Registry data as well as for overall data obtained from SEER. Consequently, the models do not necessarily

reflect the LCIS experience of non-Caucasian women, and should not be generalized to other groups.

4. Similarly, the data do not differentiate within the Caucasian sample, separating ethnicities on the basis of increased or decreased risk for invasive cancer. Consequently, in order to apply the models to more specific groups, parameter estimates specific to the groups would need to be obtained.

5. The quality of life adjustments which were ultimately used in the decision models were obtained from a large sample of third year medical students. While these individuals were familiar with the techniques utilized, and provided rather conservative adjustments, their values should not be generalized to any particular individual woman. Methods exist to elicit values from individual patients in order to fine tune the model for a given person.

6. While the Connecticut Tumor Registry data on which many parameter estimates were based is a superb registry, it is important to note that it reflects the experience of only one geographic location. Other longitudinal databases on LCIS must be developed and utilized for comparison purposes in order to validate the findings of this investigation.

Given the caveats implied by the limitations set out above, there are some implications of this research which should be considered. Given the low risk of invasive cancer associated with LCIS in this study, it is possible that LCIS is neither a precursor lesion nor a marker for increased risk of invasive disease. Perhaps it is merely a change in breast tissue similar to the fibrotic changes which occur in many women as they approach menopause. This is similar to the point made by Kinne (1992) that it is reasonable to find LCIS during the reproductive years since that is the time

when most biopsies are performed which result in benign findings; and that some involution of the lobular elements is normal with advancing age, and LCIS may follow this pattern.

If LCIS is neither a precursor lesion nor a marker for increased risk of invasive disease, what accounts for the somewhat elevated risk of invasive cancer for women under 45 found in this study? Consider the composition of the Gail formula (Gail et al., 1989) for assessing heightened breast cancer risk: one component of this formula is number of biopsies. Perhaps a finding of an association between LCIS and invasive cancer is actually a pseudo-marker, an artifact of number of biopsies performed. This perspective on LCIS would also be consistent with the repeated finding by many researchers of equal numbers of invasive cancers in the contralateral as in the ipsilateral breast. If LCIS itself is not the marker for invasive cancer, perhaps following the precise reason that a biopsy, or a number of biopsies, was performed will provide a key to the problem.

No easy answer exists as yet for management of LCIS, which continues to be found "incidentally" when women are biopsied for other purposes, since it is neither palpable nor typically visible on mammograms (Kinne, 1992). However, from this point forward, investigations will be entering into a new environment in which such factors as genetic risks will enable researchers and clinicians to better estimate risks of invasive disease for particular subgroups of patients. Additionally, the management of LCIS will no longer be restricted to the dual options of preventive bilateral mastectomy and "watch and wait," as antiestrogens (e.g., tamoxifen) have emerged as options for primary prevention. However, with more therapeutic choices, the decision regarding clinical management may only become increasingly complex, involving even more difficult quality of life issues/subjective values, including the issues of

whether and when to perform genetic screening, and the pro's and con's of antiestrogens, particularly for premenopausal women. Finally, new research has begun to question the utility of axillary lymph node dissection (ALND) in early stage breast cancers, since resulting lymphedema can cause serious decrements in quality of life (Giuliano, et al. 1994; Giulilano, et al. 1995). If LCIS is ultimately shown to act as a marker for increased risk of invasive disease in premenopausal women, it might be beneficial for surgery to be performed immediately, to avoid the possibility of serious dysfunction associated with lymphedema.

It is hoped that results of this investigation will pave the way for the more complex decision models which will be required as more diagnostic and therapeutic options evolve.

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APPENDIX A

PUBLICATIONS AND PRESENTATIONS
RESULTING FROM THE PRESENT PROJECT

- Jordan, T.J., Montgomery, R.L., & De Jager, R.L. (1995). Decision models for treatment of lobular carcinoma in situ. The European Journal of Cancer, 31a (Supp.5), 665.
- Jordan, T.J. (1995). International perspectives on breast cancer detection. In Symposium titled, Impact of culture, ethnicity, and personal history on health care decisions for breast cancer, Chaired by T.J. Jordan. Eastern Educational Research Association, Hilton Head, South Carolina.
- Jordan, T.J. (1996). Cognitive and affective assessment of populations with medical illness. Proceedings of the annual meeting of the Eastern Psychological Association, 11.
- Hummel-Rossi, B., & Jordan, T.J. (1996). Development of an instrument to measure fear of breast cancer. American Educational Research Association, New York, New York.
- Jordan, T.J., Montgomery, R.L., & De Jager, R.L. (1996). Decision models for treatment of lobular carcinoma in situ considering coexisting risks for invasive cancer. Abstracts of the 9th International Congress on Breast Diseases, 226.
- Jordan, T.J., Montgomery, R.L., Dubois, F., & De Jager, R.L. (Invited address, 1996). Decision models for the comparison of axillary node dissection and sentinel lymphadenectomy for breast cancer. Fourth International Symposium of Brussels, Brussels, Belgium.
- Jordan, T. J. (1997--accepted for presentation). Multidimensional measures of values in the treatment and prevention of breast diseases. Eastern Educational Research Association, Hilton Head, South Carolina.
- Jordan, T.J., Montgomery, R.L., & De Jager, R.L. (1997--invited paper in preparation for publication, see attached letter). Decision models for treatment of lobular carcinoma in situ in premenopausal women. The Breast Journal.
- Jordan, T.J., Montgomery, R.L., Dubois, F., & De Jager, R.L. (1997--submitted for presentation; no action on submission as yet). Decision models for treatment of early stage breast cancers considering the choice between axillary node dissection and sentinel lymphadenectomy. American Association for Clinical Oncology, Denver, Colorado.

No dissertations were completed in conjunction with this project.

The Breast Journal

May 20, 1996

Dear Colleague:

Gabriel N. Hortobagyi, MD, FACP and I had the opportunity to review your scientific work presented at the 9th International Congress on Breast Diseases/39th Annual Clinical Conferences of The University of Texas MD Anderson Cancer Center, recently, in Houston, Texas. Needless to say, we were quite impressed and believe this is an important issue to be shared with the readers of *The Breast Journal*.

We were delighted to inform you at the conference that *The Breast Journal* became the official journal of the Senologic International Society. As you may be aware, *The Breast Journal* is a bimonthly journal devoted to all aspects of breast disease. It is multidisciplinary in theme and reflects the increasing cooperation and interdependence of specialists who diagnose and treat diseases of the breast. The journal is designed to provide concise and current information on every aspect of breast disease and is enriched by an outstanding team of editorial board members from the spectrum of related specialties. *The Breast Journal* is also the official journal of the American Society of Breast Disease, making it a well recognized publication with a remarkable high subscription rate.

The 9th International Congress on Breast Diseases has chosen *The Breast Journal* for publication of your presentation. By this letter, we are inviting you to submit your manuscript for publication in *The Breast Journal* and have enclosed a Call For Papers with Instructions For Authors. The review process will be expedited and all the necessary measures taken to maintain the high quality of your scientific work. We hope that you will consider submitting your work for publication and please feel free to contact either of us with any questions.

We look forward to hearing from you soon.

Sincerely,



Shahla Masood, MD, FCAP
Editor-in-Chief



Gabriel N. Hortobagyi, MD, FACP
Editorial Board

/mft

Encl.

Editor-in-Chief

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SEER DATA: IN SITU TOTAL SAMPLE -
BREAST CANCER STUDY: FEMALES

55

Age at Diagnosis

DIAGAGE	Frequency	Percent	Cumulative Frequency	Cumulative Percent
19	1	0.0	1	0.0
20	1	0.0	2	0.1
22	1	0.0	3	0.1
24	2	0.1	5	0.2
25	3	0.1	8	0.3
26	9	0.4	17	0.7
27	5	0.2	22	0.9
28	3	0.1	25	1.1
29	5	0.2	30	1.3
30	7	0.3	37	1.6
31	6	0.3	43	1.8
32	8	0.3	51	2.2
33	13	0.6	64	2.7
34	16	0.7	80	3.4
35	25	1.1	105	4.5
36	26	1.1	131	5.6
37	23	1.0	154	6.6
38	30	1.3	184	7.9
39	27	1.2	211	9.1
40	22	0.9	233	10.0
41	38	1.6	271	11.6
42	41	1.8	312	13.4
43	50	2.1	362	15.5
44	69	3.0	431	18.5
45	65	2.8	496	21.3
46	77	3.3	573	24.6
47	91	3.9	664	28.5
48	98	4.2	762	32.7
49	102	4.4	864	37.1
50	92	3.9	956	41.0
51	82	3.5	1038	44.5
52	91	3.9	1129	48.4
53	61	2.6	1190	51.1
54	45	1.9	1235	53.0
55	49	2.1	1284	55.1
56	63	2.7	1347	57.8
57	51	2.2	1398	60.0
58	47	2.0	1445	62.0
59	49	2.1	1494	64.1
60	42	1.8	1536	65.9
61	43	1.8	1579	67.7
62	53	2.3	1632	70.0
63	56	2.4	1688	72.4
64	48	2.1	1736	74.5
65	52	2.2	1788	76.7
66	39	1.7	1827	78.4
67	35	1.5	1862	79.9
68	36	1.5	1898	81.4
69	38	1.6	1936	83.1
70	36	1.5	1972	84.6
71	27	1.2	1999	85.8
72	36	1.5	2035	87.3

SEER DATA: IN SITU TOTAL SAMPLE
BREAST CANCER STUDY: FEMALES

Age at Diagnosis

DIAGAGE	Frequency	Percent	Cumulative Frequency	Cumulative Percent
73	27	1.2	2062	88.5
74	31	1.3	2093	89.8
75	30	1.3	2123	91.1
76	27	1.2	2150	92.2
77	19	0.8	2169	93.1
78	26	1.1	2195	94.2
79	16	0.7	2211	94.9
80	21	0.9	2232	95.8
81	12	0.5	2244	96.3
82	17	0.7	2261	97.0
83	7	0.3	2268	97.3
84	13	0.6	2281	97.9
85	18	0.8	2299	98.6
86	7	0.3	2306	98.9
87	6	0.3	2312	99.2
88	5	0.2	2317	99.4
89	4	0.2	2321	99.6
90	3	0.1	2324	99.7
91	1	0.0	2325	99.7
92	1	0.0	2326	99.8
94	2	0.1	2328	99.9
96	1	0.0	2329	99.9
98	2	0.1	2331	100.0

Race/Ethnicity

ETHNIC	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	1891	81.1	1891	81.1
1	129	5.5	2020	86.7
2	124	5.3	2144	92.0
3	4	0.2	2148	92.1
4	20	0.9	2168	93.0
5	65	2.8	2233	95.8
6	11	0.5	2244	96.3
7	14	0.6	2258	96.9
8	12	0.5	2270	97.4
9	61	2.6	2331	100.0

Marital Status at Diagnosis

MARSTAT	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	150	6.4	150	6.4
2	1599	68.6	1749	75.0
3	22	0.9	1771	76.0
4	140	6.0	1911	82.0
5	368	15.8	2279	97.8
9	52	2.2	2331	100.0

Year of First Diagnosis

YEARDIAG	Frequency	Percent	Cumulative Frequency	Cumulative Percent
73	324	13.9	324	13.9
74	433	18.6	757	32.5
75	601	25.8	1358	58.3
76	542	23.3	1900	81.5
77	431	18.5	2331	100.0

Location on Body of Primary Site

SITE2	Frequency	Percent	Cumulative Frequency	Cumulative Percent
740	48	2.1	48	2.1
741	139	6.0	187	8.0
742	109	4.7	296	12.7
743	48	2.1	344	14.8
744	457	19.6	801	34.4
745	111	4.8	912	39.1
746	8	0.3	920	39.5
748	263	11.3	1183	50.8
749	1125	48.3	2308	99.0
799	23	1.0	2331	100.0

Appendix C:

Appendix C

AGE AGE AT DX

59

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
	27	1	.1	.1	.1
	28	1	.1	.1	.2
	32	1	.1	.1	.4
	33	7	.8	.8	1.2
	34	1	.1	.1	1.3
	35	6	.7	.7	2.0
	36	7	.8	.8	2.9
	37	10	1.2	1.2	4.1
	38	12	1.4	1.4	5.5
	39	12	1.4	1.4	7.0
	40	13	1.6	1.6	8.6
	41	16	1.9	1.9	10.5
	42	29	3.5	3.5	14.0
	43	29	3.5	3.5	17.5
	44	32	3.9	3.9	21.3
	45	25	3.0	3.0	24.3
	46	41	4.9	4.9	29.3
	47	51	6.1	6.1	35.4
	48	44	5.3	5.3	40.7
	49	40	4.8	4.8	45.5
	50	40	4.8	4.8	50.4
	51	38	4.6	4.6	54.9
	52	34	4.1	4.1	59.0
	53	29	3.5	3.5	62.5
	54	13	1.6	1.6	64.1
	55	19	2.3	2.3	66.4
	56	17	2.0	2.0	68.4
	57	13	1.6	1.6	70.0
	58	21	2.5	2.5	72.5
	59	21	2.5	2.5	75.1
	60	16	1.9	1.9	77.0
	61	13	1.6	1.6	78.6
	62	9	1.1	1.1	79.6
	63	16	1.9	1.9	81.6
	64	12	1.4	1.4	83.0
	65	13	1.6	1.6	84.6
	66	11	1.3	1.3	85.9
	67	12	1.4	1.4	87.3
	68	15	1.8	1.8	89.2
	69	15	1.8	1.8	91.0
	70	6	.7	.7	91.7
	71	7	.8	.8	92.5
	72	4	.5	.5	93.0
	73	11	1.3	1.3	94.3
	74	5	.6	.6	94.9
	75	6	.7	.7	95.7
	76	4	.5	.5	96.1

AGE AGE AT DX

77	5	.6	.6	96.7
78	6	.7	.7	97.5
79	3	.4	.4	97.8
80	1	.1	.1	98.0
81	2	.2	.2	98.2
82	4	.5	.5	98.7
83	2	.2	.2	98.9
84	1	.1	.1	99.0
85	1	.1	.1	99.2
86	1	.1	.1	99.3
87	3	.4	.4	99.6
88	1	.1	.1	99.8
89	1	.1	.1	99.9
95	1	.1	.1	100.0

Total	830	100.0	100.0
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Mean 53.060

Valid cases 830 Missing cases 0

DATE_DX YEAR OF DIAGNOSIS

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
	73	18	2.2	2.2	2.2
	74	15	1.8	1.8	4.0
	75	29	3.5	3.5	7.5
	76	13	1.6	1.6	9.0
	77	30	3.6	3.6	12.7
	78	10	1.2	1.2	13.9
	79	16	1.9	1.9	15.8
	80	24	2.9	2.9	18.7
	81	21	2.5	2.5	21.2
	82	26	3.1	3.1	24.3
	83	23	2.8	2.8	27.1
	84	38	4.6	4.6	31.7
	85	44	5.3	5.3	37.0
	86	49	5.9	5.9	42.9
	87	72	8.7	8.7	51.6
	88	49	5.9	5.9	57.5
	89	66	8.0	8.0	65.4
	90	65	7.8	7.8	73.3
	91	62	7.5	7.5	80.7
	92	45	5.4	5.4	86.1
	93	55	6.6	6.6	92.8
	94	60	7.2	7.2	100.0
	Total	830	100.0	100.0	

Mean 86.248

Valid cases 830 Missing cases 0

DATE_LST YEAR LAST SEEN OR DEATH

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
	75	1	.1	.1	.1
	77	3	.4	.4	.5
	78	1	.1	.1	.6
	79	2	.2	.2	.8
	80	1	.1	.1	1.0
	81	2	.2	.2	1.2
	82	3	.4	.4	1.6
	83	2	.2	.2	1.8
	84	5	.6	.6	2.4
	85	8	1.0	1.0	3.4
	86	13	1.6	1.6	4.9
	87	7	.8	.8	5.8
	88	15	1.8	1.8	7.6
	89	15	1.8	1.8	9.4
	90	20	2.4	2.4	11.8
	91	9	1.1	1.1	12.9
	92	28	3.4	3.4	16.3
	93	50	6.0	6.0	22.3
	94	126	15.2	15.2	37.5
	95	240	28.9	28.9	66.4
	96	279	33.6	33.6	100.0
	Total	830	100.0	100.0	

Mean 93.917

Valid cases 830 Missing cases 0

DECISION ANALYSIS EXERCISE: UTILITY VALUES

L.M., a 35-year old, married woman, has returned from a follow up visit to her physician. The physician gave her the results of a pathology report from a breast biopsy done on L.M. one week prior. The report showed *lobular neoplasia* in one breast. *Lobular neoplasia* is not breast cancer. However, it increases a woman's chance of developing breast cancer in one or both breasts by a factor of 3 (i.e. 300% greater than average risk, or 3 to 1 risk ratio).

L.M. is faced now with making a choice (decision) among four possible courses of action:

1.) She can "watch and wait" which means that she will be followed with frequent mammograms (2 to 4 times per year) as well as with frequent physical exams for the rest of her life, in the hope that if she develops breast cancer, her cancer will be detected early enough to achieve a cure through mastectomy and possible adjuvant therapies (e.g., chemotherapy, hormone therapy.) However, the "watch and wait" approach will not necessarily catch a cancer early enough to prevent death from breast cancer. Also, mastectomy for cancer (rather than for prevention) typically involves lymph node dissection, which can result in disabling lymphadenopathy in the adjacent arm(s).

2.) She can elect "preventive bilateral mastectomy" (surgical removal of both breasts), which will virtually ensure that she will never develop breast cancer. Preventive bilateral mastectomy means doing surgery in the absence of invasive disease: Therefore, she will not need to have her lymph nodes dissected, will not risk lymphadenopathy, and will not require chemotherapy or hormone therapy for metastatic disease. She can elect to have preventive bilateral mastectomy without breast reconstruction, which means that she will have a mastectomy scar on each side of her chest.

3.) She can elect "preventive bilateral mastectomy" (exactly as per choice #2 above) with breast reconstruction. Reconstruction will confer the same protection against breast cancer. However, it will require more hospital time and more hospital visits to complete the reconstructive process. Reconstruction after "preventive bilateral mastectomy" will result in a good cosmetic outcome.

4.) Finally, she can elect lifelong medical treatment with Tamoxifen, an antiestrogen therapy with documented positive results in cancer patients, but data about efficacy in breast cancer prevention are still being collected. It is only theorized at this point that Tamoxifen might play a role in reducing breast cancer in patients specifically with *lobular neoplasia*. If L.M. elects this option, she would be on an experimental protocol, and would be required to have the frequent mammograms and physical exams required under the "watch and wait" option. Tamoxifen has been shown to increase the risk of endometrial cancer which is highly curable.

Directions:

For the purposes of this exercise, try to place yourself in the position of the patient, L.M. Please attempt to do this to the best of your ability regardless of whether you are male or female. While this might seem strange, it is very valuable to be able to "place yourself in the patient's shoes" in order to help patients think through difficult or complex treatment options.

Now turn to the next page and complete the exercise.

Page 2. Task 1:

Consider the fact that most decisions made by an individual take into account other peoples' opinions. In the case of L.M., let us begin by assuming that at least three peoples' opinions will be considered: Her own, her physician's, and her husband's. How much importance do you believe L.M. will place on her own opinion, that of her physician, and that of her husband? Please indicate this by assigning a weight from 0 (not important at all) to 100 (maximally important) to each of the three. You may use the same weight more than once.

Now, think about whether you believe that the opinions of some other people will play a role in L.M.'s decision. Who might they be? There are two blanks for you to fill in to indicate the other people whose opinions might be important to L.M. Please remember to assign weights to these other peoples' opinions if you have filled in one or two of these blanks.

Person	Importance of opinion 0 - 100	Person	Importance of opinion 0 - 100	Person	Importance of opinion 0 - 100	Person	Importance of opinion 0 - 100
Patient, L.M.		Physician		Husband		Other	

Task 2:

Now, consider each of the four treatment options confronting L.M. On a scale from 0 (least valued) to 10 (most valued), assign a value to each of the treatment options from the perspective of the patient, L.M. You may assign the same value more than once if necessary. After you complete the "valuing" from L.M.'s perspective, please go through the same process to assign values you believe would be held by her physician, and then by her husband. As you do this valuing, please remember that it is completely independent of the weights you assigned to each person in Task 1. If you have added additional people to L.M.'s treatment decision, please be sure to assign values to the four treatment options from their perspectives as well.

Treatment:	L.M., the patient 0-10	Physician 0-10	Husband 0-10	Other 0-10
Watch and Wait				
Tamoxifen, and wait				
Bilateral Mastectomy with reconstruction				
Bilateral Mastectomy without reconstruction				

Please indicate your gender (M), (F) Your age _____ Optional: Have you or a member of your family had breast cancer? Yes _____ No _____