# CANCER POLICY: RESEARCH AND METHODS

# Cancer Treatment and Research

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# Cancer Policy: Research and Methods

*edited by*

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# Foreword

Policy and outcomes studies represent a new area of research in oncology. Understanding the factors that affect quality of life, costs of care, patterns of care, and outcomes in oncology is important to providing comprehensive care.

Quality of life research, the subject of the chapter by Reifel and Ganz, is the most established area of health services in oncology, with the development of three generations of self-administered instruments. At the other end of the spectrum, utility assessment, described by Chapman and Elstein, is the newest area of study, with investigators developing innovative ways to query patients about the relative importance of alternative health states that are potential outcomes for the individual patient. These two chapters provide complementary assessments of health status of individual patients, by investigating how the patients might feel in the future (utility assessment) as well as describing how the patient felt in the past (quality of life assessment).

Costs of cancer care have become one of the major determinants of the type and intensity of patient care. Waters describes the potential cost savings associated with development of new technologies such as peripheral blood stem transplantation. Given the importance of costs to managed care organizations and policy makers, Schulman and Boyko illustrate the feasibility of collecting economic information during the phase III clinical trial setting, an area of research that is of direct practical importance to policy makers who are affiliated with the National Cancer Institute cooperative clinical trial study groups. An additional source of cost information are the tumor registries of individual states in conjunction with the Federal Medicare files, as illustrated by Desch and Penberthy. While many recent studies focus on the costs of cancer care, few address the value of these services. Bitran provides new insights into the costs of cancer care in the community setting, an area of increasing importance in this era of managed care. Terminal care is among the most costly and poorest developed area of oncology care. Smith provides a nice overview of the breadth of research in this new area, with references to recently completed landmark studies such as the Study to Understand the Prognoses, Preferences, Outcomes, and Risks of Treatment (SUPPORT) study.

Health services research studies often address difficult and controversial topics in oncology. Pfister and colleagues describe an example of one difficult area, the study of head and neck cancer patients, where most of the previous research has been directed to improvements in survival. Similarly, Hynes and Bastian illustrate a second problematic area, breast cancer care ( a common cancer) in the VA medical system (where women are decidedly uncommon). Racial/ethnic variations in oncology care mirror those found in almost all aspects of medicine. Horner provides some of the first evidence of large racial/ethnic variations in prostate cancer care, raising concern over the adequacy of care for African American males with prostate cancer. Dale uses focus group data to identify some of the cultural causes of variations in prostate cancer care. Finally, a fitting close to this first edition of cancer policy is the chapter on informed decision making for women who are contemplating hormone replacement therapy by Bastian and others. Health

services is meant to be both a productive area of research as well as a discipline that improves patient decision making. In sum, the dozen chapters in this edition highlight some of the important areas of health services research in oncology. We are pleased to have had the opportunity to edit this work.

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# QUALITY OF LIFE RESEARCH: CLINICAL APPLICATIONS

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## Introduction

Concern over the rising costs of health care in the United States has focused attention on the young discipline of health services research. While outcomes of disease and treatment have always been important in medical care, at least implicitly, the new discipline of health services research has broken down the concept of outcomes explicitly and developed ways to measure them. The Behavioral Model of Health Services Use (Figure 1) provides a useful conceptual framework for understanding the health care system, including the factors that influence people accessing health care, their use of health services, and health outcomes. Health outcomes include consumer satisfaction, evaluated health status, and perceived health status. Consumer satisfaction refers to patients satisfaction with their experience with the health care system. Evaluated health status represents those aspects of an individual's health that can be observed and measured such as mortality, organ dysfunction, or disability. Perceived health status is an individual's own perception about his or her health and how it impacts on other aspects of life. Perceived health status is used synonymously by health services researchers as health related quality of life or simply quality of life (QOL.)

QOL is a multidimensional construct that includes somatic symptoms, functional ability, emotional well-being, social functioning, sexuality and body image, treatment satisfaction and global QOL. [1-4 ] While other measures such as pain scales, mood scales, measures of ability to fulfill the activities of daily living,

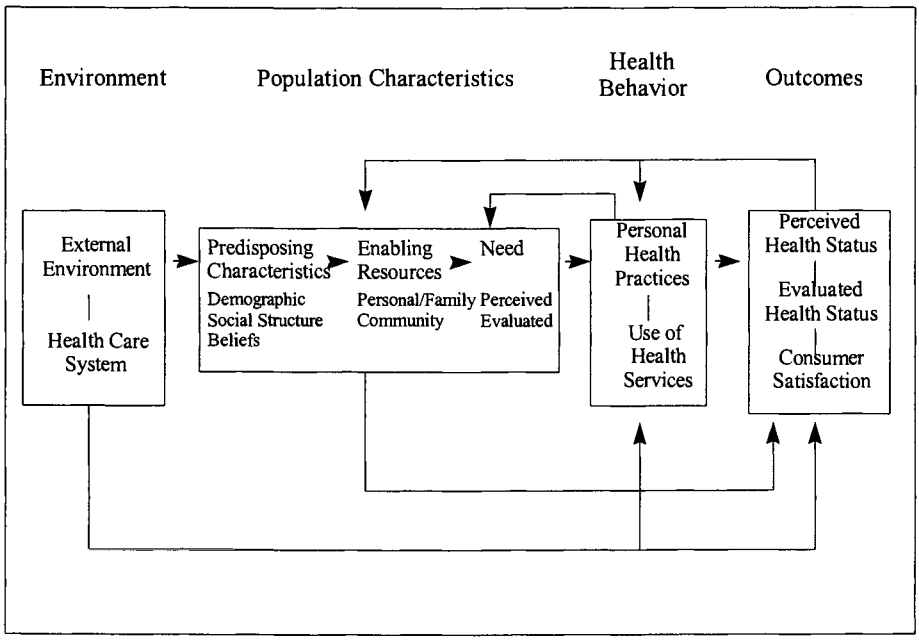


**Figure 1.** A Behavioral Model of Health Services Use

and toxicity ratings provide useful information, when used individually, they do not measure QOL. First of all, these other measures are not multidimensional; they deal with only one or two aspects of a patient's experience with the illness or its treatment. Secondly, QOL is affected by both the treatment and the disease. For example, toxicity ratings assess only the impact of the treatment, not the disease, on the patient. Finally, QOL measures emphasize the impact of symptoms on patients' functional status and well-being. QOL assessment provides a more comprehensive evaluation of the impact of illness and its treatment on patients than a unidimensional measure.

Especially when treating patients for whom no cure is available, oncologists often implicitly assess the potential impact of therapy on patients' QOL in making treatment decisions. For example, the Karnofsky Performance Status, an expert rating of patients' functional status, has been used for many years in clinical trials and has been shown to be a strong predictor of survival in certain patient populations, most notably patients with lung cancer. [5, 6] However, several studies demonstrate that caregivers and providers are poor proxy raters of the patient's QOL. [7-9] And, while the physician-rated Karnofsky Performance Status has been significantly correlated with patients' self-reported QOL, the correlation coefficients account for less than 50% of the variability in patient ratings of QOL, suggesting that physical performance is only one factor that contributes to QOL and is

therefore an incomplete assessment. [7, 9,10] Accordingly, oncologists must begin to move beyond traditional physician-rated measures to those that more accurately reflect the patient's assessment. This is particularly true in the palliative care setting.

This chapter will focus on how findings from QOL research can be applied to clinical practice. First, we will examine some of the tools of QOL research and the limitations of the current assessment technology. Then, we will review some examples of clinical research that have incorporated QOL measures and examine how the results of these trials can be used in clinical practice to help with treatment decisions for individual patients. Finally, we will explore how oncologists may directly apply this expanding technology to their practices in the future by ordering a "Quality of Life Test" to help guide their clinical management of patients.

## How to Measure QOL and Evaluate the Results of QOL Research

The measurement of QOL is a complex task that draws on the fields of social science research and psychometrics. [5, 11,12] The tools used to measure QOL, in general, are self-administered questionnaires that have undergone extensive testing of their reliability and validity. This means that they meet rigorous standards of reproducibility and accuracy. These questionnaires can be administered to patients as either pen and pencil surveys, over the telephone, or via face-to-face interviews. Most of the widely accepted tools are multidimensional. The tools that are currently available for clinical research include measures of general health status that can be applied to a variety of clinical situations, cancer-specific instruments, cancer site-specific instruments, and symptom-oriented scales (Table 1).

### *Challenges to the Clinical Application of QOL Research*

In developing or selecting a QOL instrument for use in a research or clinical setting, there are several methodological considerations that need to be addressed to ensure the validity of the data obtained, as well as its clinical relevance. While many general and cancer-specific QOL instruments have been developed and validated for use in patients with cancer, these have been tested primarily in research settings with adequate staff to ensure completion of the questionnaires and to minimize missing data. Increasingly, these QOL measures have been included in clinical treatment trials, where there have been more frequent problems with missing data. This is an especially serious problem in patients with deteriorating physical status, often the patients in whom there is greatest interest in measuring QOL. [13] For example, in a study of QOL in lung cancer patients with a Karnofsky Performance Status greater than 50 at entry, Ganz *et al* noted that patients with the lowest performance status had a disproportionately low rate of self- administration of the QOL questionnaire, and 30% of all the questionnaires were actually

completed by the interviewer administering it as patients were unable to complete it themselves. [13]

**Table 1.** Instruments Used to Measure Quality of Life in Cancer Patients

| |
|---|
| *General Health Status Instruments* |
| Medical Outcomes Study Instruments (SF-20 and SF-36] |
| McMaster Health Index Questionnaire (MIUQ) |
| Sickness Impact Profile (SIP) |
| *Cancer-Specific Instruments* |
| Cancer Rehabilitation Evaluation System (CARES) |
| Functional Living Index Cancer (FLIC) |
| Functional Assessment of Cancer Therapy (FACT) |
| European Organization for Research and Treatment of Cancer Quality of life Questionnaire (EORTCQLQ-30) |
| Southwest Oncology Group Quality of life Questionnaire |
| *Cancer Site-Specific Instruments* |
| Breast Cancer Chemotherapy Questionnaire |
| Performance Parameter (Head and Neck) |
| *Symptom-Oriented Scales* |
| Rotterdam Symptom Checklist |
| Memorial Pain Assessment Card |
| Morrow Assessment of nausea and Emesis |

As patients' functional status deteriorated during the course of their disease, self-administration rates declined and missing data were an even greater problem. Because of missing data, these investigators were unable to perform their intended comparison of QOL between two treatment arms (supportive care alone and supportive care with combination chemotherapy). This has been noted in a number of trials and results from a combination of patient and staff-related problems. [14-16] In July 1996, the major international cooperative clinical trials groups met at a workshop in Switzerland, with representation of methodologists and statisticians, and a forthcoming supplement to *Statistics in Medicine* from this workshop will address the problem of missing QOL data in clinical trials in more detail. Compliance with QOL questionnaire completion remains an important quality control problem within the clinical trial setting, as well as a data analysis challenge. Although these problems may be peculiar to the clinical trial setting, they are probably also relevant to sicker patients in the clinical practice setting.

Another methodologic concern in QOL research lies in the interpretation of differences in scores on QOL scales over time. In clinical trials, differences

between groups of patients are examined over time and comparison of the groups can be statistically significant. In clinical practice, a more important question relates to changes in an individual patient's scores. [17] What does a 2-point change in emotional well-being on a particular QOL instrument mean in an individual patient assessed 4 weeks apart? Does it represent a meaningful change in that patient's emotional well-being? If the change was observed after receiving a particular treatment, should a 2-point difference be enough of a change to recommend the treatment? While work has been done in trying to ascertain the minimal clinically important difference on a QOL scale for patients with other chronic illnesses, such as congestive heart failure, it remains to be established for QOL instruments commonly used in oncology. [18]

Finally, QOL instruments are language and culture-specific so their validity must be established in each new patient population. Patients' responses to illness are culturally mediated,[19,20] and their perception of illness and its effect on a QOL dimension are also subject to culture-specific constructs. Responses to a questionnaire depend upon the patient's interpretation of the questions. Therefore, a QOL instrument must be tested for reliability and validity upon each translation into a new language. In a city like Los Angeles, for example, that has a linguistically and culturally diverse population, having QOL instruments that are reliable and valid for all patients represents an important challenge.

*Application of QOL Research Findings to Clinical Practice*

In the last few years, the number of cancer clinical trials including QOL outcomes has increased dramatically. Fewer than 5% of clinical trials reviewed by the Department of Health and Human Services in 1982 included QOL measures. The United States Food and Drug Administration (FDA) now requires both a benefit to QOL as well as improved survival for approval of new anticancer drugs. [21] Since 1992, the National Cancer Institute of Canada has mandated that QOL outcomes be included in all of its Phase III clinical trials. [22] Also, as of 1995, 15% of active ECOG trials have included an evaluation of QOL, and many of the phase III trials of the other US cooperative groups also include QOL assessment. So, while at present only a small number of published clinical trials have included QOL outcomes, in the near future, oncologists will have an increasing amount of information on patients' QOL in addition to the traditional endpoints of survival and response. Recently, an outcomes working group from ASCO defined a number of these additional outcomes. [23]

So, how can the results of QOL studies be applied to the clinical practice of oncology? First, QOL instruments can be used to identify baseline patient characteristics that are predictive of prognosis, response to treatment, and the likelihood of experiencing treatment-related toxicities. Second, perhaps the greatest utility of QOL data to the oncologist is in advising patients on treatments with comparable survival benefits but differing effects on QOL. And, third, the findings of QOL research can be helpful to those patients for whom QOL is of primary

importance when deciding between palliative therapies that involve tradeoffs between survival and QOL.

*Using Baseline QOL Data to Help Predict Prognosis*

QOL assessment can be used to identify baseline patient characteristics that are predictive of prognosis, response to treatment, and the likelihood of experiencing treatment-related toxicities. For example, in patients with metastatic non-small cell lung cancer, Ganz et al observed a significant relationship between patients' QOL at diagnosis and their subsequent survival. [24] In this study, Ganz et al administered the Functional Living Index-Cancer (FLIC), a validated cancer-specific measure of QOL, to 40 patients with metastatic non-small cell lung cancer, with a Karnofsky Performance Status of 50 or greater, who were subsequently randomized to supportive care or supportive care with combination chemotherapy. The FLIC contains 22 questions which address somatic symptoms, functional ability, social functioning, emotional well being, treatment satisfaction, sexuality, and global QOL and provides a summary score between 22 and 154, where a higher score represents a better QOL. The researchers dichotomized the data into two groups, a "high" FLIC score group and a "low" FLIC score group (a high FLIC score was defined as a score of greater than or equal to 106.5 and a low score was less than 106.5). Patients who scored high on the FLIC at baseline (prior to any treatment,) had a median survival of 24 weeks compared with 11.9 weeks for the patients who had a low score. In a Cox regression model controlling for treatment assignment, histology, metastatic sites, weight loss, and performance status,
baseline QOL significantly predicted survival time.

The results of this study suggest that patients with metastatic non-small cell lung cancer and low QOL at diagnosis are likely to have a worse outcome regardless of treatment. Routine assessment of QOL in patients with advanced lung cancer could provide a more systematic approach to determining which patients are unlikely to benefit from chemotherapy, helping the physician instead to focus on supportive care interventions for the patient and family. Several of the cancer-specific tools listed in Table1 may be useful for this purpose. In less severely ill patients, such as newly-diagnosed breast cancer patients, baseline QOL assessment may assist in the identification of patients at high risk for difficulties coping with treatment, and later with "cancer-survivorship." [25] As more clinical trials include QOL assessments, there will be an enlarging database of baseline QOL scores that can be used to identify patients at risk for poor outcomes.

*QOL Research to Help in Deciding Between Treatments of Comparable Efficacy*

Perhaps the greatest potential use of data from QOL research for the practicing oncologist is in advising patients on treatments with comparable effects on survival. Under these circumstances, the relative impact of the treatments on patients' QOL is

of paramount importance. Clinical predictions of the impact of treatments on QOL are frequently inaccurate. For example, in the treatment of early stage breast cancer, physicians had predicted that women who received breast conserving surgery followed by radiation therapy would have a better QOL than women treated with mastectomy. However, several research groups have found no significant differences in overall QOL between women who received mastectomy or breast-conserving surgery as primary treatment for early-stage breast cancer. [26-29] Thus, clinical judgment does not appear to be an accurate substitute for patients' experience of cancer and its treatment. Whenever possible, patient preferences should be assessed, and physicians should provide data from QOL studies to guide patients in making decisions about their treatment.

The treatment of localized prostate cancer is another area in which the results of QOL research can be used to help guide medical decision making. Both radical prostatectomy and radiation therapy appear to have comparable efficacy in treating localized prostate cancer. While the data from randomized clinical trials are limited, non-randomized studies of patients with localized prostate cancer have demonstrated similar 10-year disease-specific survival rates and overall survival rates (approximately 85% and 60% respectively) for patients treated with radical prostatectomy or radiation therapy[30],making differences in the impact of these treatments on QOL extremely important to patients trying to decide which therapy to pursue. In a descriptive study, Lim *et al* asked all patients with localized prostate cancer who received definitive treatment at their institution with radical prostatectomy or radiation therapy between January 1992 and January 1994 to complete the FLIC, the Profile of Mood States (a 65 item scale of six moods, depression, anger, tension, confusion, fatigue and vigor,) and a symptom inventory which evaluated urinary symptoms, sexual dysfunction, and bowel dysfunction. [31] Among patients who completed the questionnaires, 89 patients who underwent radical prostatectomy (65%) and 46 who underwent radiation therapy (77%), there was no difference in the FLIC summary score. However, the patients who were treated with radical prostatectomy had significantly worse symptoms of urinary incontinence and worse sexual function scores compared with patients treated with radiation therapy. On the other hand, patients treated with radiation therapy were more likely to report problems with loose stools than patients treated with radical prostatectomy. In both groups, problems with incontinence, sexual functioning, and bowel functioning were significantly associated with higher scores for depression, tension, and fatigue on the Profile of Mood States, so they do appear to impact QOL.

In a similar study, Litwin *et al* compared QOL outcomes in 214 men with clinically localized prostate cancer treated with either radical prostatectomy, radiation therapy, or observation with 273 randomly selected, age-matched, zip code-matched controls without prostate cancer, all enrollees of the same managed care plan in California. [32] Of the men with clinically localized prostate cancer, 98 (46%) had been treated with radical prostatectomy, 56 (26%) received radiation therapy, and 60 (28%) were observed without further treatment. All men were mailed a questionnaire which included the RAND 36-item Short Form (a general

measure of QOL), two cancer-specific measures of QOL, the Cancer Rehabilitation Evaluation System Short Form (CARES-SF) and the Functional Assessment of Cancer Therapy (FACT), as well as newly developed questions specific to function and bother in the sexual, urinary, and bowel areas. Litwin *et al* also found no significant differences in overall QOL as measured by the RAND 36-item Short Form, the CARES-SF, or the FACT between the treatment groups or between men with prostate cancer compared with the age-matched controls. Men with prostate cancer reported more problems with sexual functioning on the CARES-SF and the specific function questions than men without prostate cancer. However, men who underwent radical prostatectomy were statistically indistinguishable from those treated with radiation. With regards to urinary function though, patients treated with surgery scored significantly worse than patients who received radiation or observation, as well as the controls. As expected, radiation therapy patients did experience worse bowel function and bowel bother than the comparison patients without prostate cancer.

While the results of these studies should be interpreted with caution due to methodological limitations, both provide useful information to clinicians advising patients on a choice of treatment for localized prostate cancer. Because of non-responder bias, these studies may underestimate the actual difference in QOL between the treatment groups. While Litwin *et al* had a high response rate (79%) among the patients with prostate cancer, only 46% of the comparison patients responded. Given the low response rate among the comparison group, their results may be biased as men who responded may be more or less likely to report problems with QOL than other men, In addition, both studies measured QOL at only one point in time. Longitudinal data would be particularly helpful in as we do not know if the scores reported represent a change from study participants' baseline QOL. As symptoms of incontinence, sexual function, and bowel function often change with time after treatment for prostate cancer, it is likely that with increasing time post-treatment, QOL changes as well. In spite of these limitations, these studies provide valuable information for the clinician. The clinical implications of these results are that there are few differences in survival or QOL when comparing radical prostatectomy and radiation therapy for localized prostate cancer. However, the two treatments affect QOL in different ways. By describing these differences to patients, clinicians can provide patients with important information that will allow them to make choices about treatments that are informed and most congruent with their values.

### *QOL Research Helps with Tradeoffs Between Survival and QOL for Palliative Therapy*

Making decisions that involve tradeoffs between survival and QOL are a frequent part of oncology practice. For many patients, treatment decisions are based exclusively upon a desire to prolong survival. However, for some patients, preserving QOL, even at the expense of length of life, is of paramount importance.

Generally, physicians rely on their anecdotal experience with various treatment regimens and their perception of patients' QOL to advise patients. However, as discussed earlier, providers are generally poor judges of patients' perceived QOL. Hence, randomized clinical trials that compare the effects of palliative treatments on survival and QOL provide important information that is more likely to truly reflect the comparative impact of treatments on QOL. This then allows physicians to share this information with patients to help them with difficult and personal choices.

One such trial by Chodak *et al* examines the differences in survival and QOL for men with advanced prostate cancer treated with antiandrogen therapy or castration (medical or surgical). [33] In this multicenter trial, 243 patients were randomized to each of two treatment arms. One group received bicalutamide and the other castration, either via orchiectomy or monthly depot injections of goserelin. QOL was measured every 3 months for up to 1 year or until disease progression, using a 33-item questionnaire assessing activity limitation, confinement to bed, emotional well-being, overall health, pain, physical capacity, sexual function and interest, social functioning, and vitality. With a median follow-up of 86 weeks, median survival was not reached in either treatment arm; however, disease progression was lower for the castration group (43% vs. 33%, P=0.002) and survival analysis also favored castration (probability of death 1.29 for bicalutamide compared to castration, 95% CI, 0.96 to 1.72.) All patients reported increased physical capacity and vitality, less limitation of activity, less time in bed, and less pain, regardless of treatment; however, bicalutamide treated patients maintained baseline sexual interest and functioning throughout treatment while patients treated with castration did not. And, though it was only statistically significant during the first month of treatment, bicalutamide-treated patients reported a greater sense of emotional well-being than patients treated with castration. The clinical implications of these data are that both bicalutamide and castration improve QOL for patients with advanced prostate cancer, though patients treated with bicalutamide may have higher sexual functioning and a greater sense of emotional well-being, but at a potential cost to both progression-free survival and overall survival.

*What does the future hold?*

The time is not too far off when oncologists will be able to order a "QOL Test" to help them evaluate a patient, much in the way they order bone scans or chest x-rays today. Using QOL instruments in clinical practice will allow oncologists to obtain baseline information about patients and, by applying the results of QOL research as we described earlier, use it to help in predicting prognosis, plan treatment, and anticipate patients' needs for social or psychological support. QOL instruments may also be used, when administered at regular intervals throughout a patient's treatment, to assess systematically the effect of palliative therapy on QOL. Currently, tumor markers or radiologic studies are used to evaluate treatment response. However, when the goal of therapy is palliation, changes recorded by a patient on a QOL instrument may be a more sensitive and meaningful way of evaluating patient response.

The Cancer Rehabilitation Evaluation System (CARES) is one such instrument that has been validated as a measure of QOL in research settings, [34, 35] and, though it has not yet been formally studied in clinical settings, it has been used in physicians' practices and as part of a comprehensive evaluation for a psychosocial support program for patients with cancer. [36] The CARES is a 139-item questionnaire of which the first 88 are completed by all patients and the remaining 51 only as they apply, to patients' specific circumstances. Patients rate each problem on a scale of 0 to 4 (0="not at all" [no problem] and 4="very much" [severe problem]) and are asked to indicate by circling "Yes" or "No" if they would like help with the problem. The CARES has demonstrated excellent test-retest reliability, and it has been validated for use in clinical trials as a comprehensive measure of QOL in patients with cancer in studies comparing it with other instruments including the Symptom Checklist-90, the Dyadic Adjustment Scale, the Karnofsky Performance Status, and the FLIC. In addition, it has been shown to be a useful companion to a comprehensive interview by a trained medical social worker in identifying the rehabilitative needs of patients. To incorporate the CARES more efficiently in the clinical setting, the CARES responses to the questionnaire from the patient are entered into a computer program that scores the instrument and provides an individualized clinical report with the patient's score on the CARES Global Scale, as well as the five summary scales (Physical, Psychosocial, Medical Interactional, Marital, and Sexual), compared to scores from a normative sample of cancer patients. In addition, specific problems are listed, along with information specifying whether the patient has indicated wanting help with the problem.

Although QOL assessment is on the verge of becoming available for use in clinical practice, further testing in the clinical setting is required, and several issues need to be addressed. First, to date, QOL instruments have been used only in the research setting where differences in group outcomes have been the primary interest. For evaluation of individual subjects, reliability standards are much higher, In addition, QOL instruments must be sensitive enough to detect changes over time in an individual patient, Also, for QOL instruments to be applicable in clinical practice, it is critical to determine how to interpret a clinically significant change. Finally, to be useful in the clinical setting, QOL instruments must be "user-friendly". Patients must be able to complete them without requiring substantial assistance from a physician's office support staff, and the results must be available in a format that is useful to the clinician.

## Conclusion

The Behavioral Model of Health Services Use establishes a comprehensive framework from which to view health outcomes. Multiple factors impact the health outcomes of QOL, evaluated health status, and consumer satisfaction. These factors include not only patients' health behavior, including their personal health practices

and utilization of health services, but also patient characteristics, such as their perceived health needs, enabling resources (e.g. access to transportation) and health beliefs. In addition, both the health care system and the external environment influence patient characteristics, health behavior, as well as health outcomes. Thus, both in measuring and when trying to improve health related QOL, it is important to consider not only the effects of the illness and treatment on patients' QOL but also those experiences beyond their interactions with the health system which may affect it. In addition, the impact of treatment on QOL will be affected by patients' baseline QOL, and this too must be considered when applying the results of QOL research to clinical practice. For example, patients with poor performance status at the outset of their illness, even as they are potentially more vulnerable to disability, may have already accommodated to a lower functional status and thus not perceive as great a change in QOL as someone with good performance status at baseline. Health outcomes, in turn, feed back on patients' health behavior and perceived need for health care and health beliefs. The Behavioral Model of Health Services Use demonstrates many areas in which clinicians and researchers can intervene to improve cancer outcomes. And, while developing more curative treatments for cancer is crucial, improving oncology outcomes will require a comprehensive approach directed at every level of this model.

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# UTILITY ASSESSMENT: METHODS AND RESEARCH

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## Introduction

Many medical decisions are strongly influenced by the goals and preferences of the particular patient. Because the evidence favoring specific treatments for many cancers is mixed, some investigators have argued that patient preferences are an important factor in these treatment decisions.[1,2] The emphasis on patient involvement introduces the question of how to measure patient preferences and how to incorporate them into a decision.

What information is needed to make this decision? According to a decision making strategy known as utility theory, the patient and clinician need to consider four things. First, what are the available options? Second, what are the possible outcomes of each of these alternatives? Third, how likely is each of these outcomes, given each treatment option? Utility theory quantifies these uncertainties as probabilities. Finally, how good or bad would it be to experience each of these outcomes? In the vocabulary of this approach, what are the patient's utilities for each outcome?

Once the treatment options and the possible resulting outcomes are already specified, the probabilities of each outcome could be drawn by the clinician from clinical studies or trials of the treatment [3], and these estimates could be modified to account for local clinical experience or the patient's characteristics (such as age and comorbidities). The utilities, the final component, are not yet known because they depend on the patients personal preferences. This step can be completed through utility assessment, a process that involves some type of structured questionnaire or interview.

## The Purpose of Utility Assessment

Utility assessment is inherently a prospective activity. Because a patient's treatment decision may result in a set of outcomes, however, he/she must judge now what his preferences will be if he/she ever experiences one of these health states. These preference judgments must be compared with the value of his/her current health state; a state he/she has already experienced. Consequently, utility assessment in clinical problems always involves the consideration of at least some health states that are not currently being experienced.

Utility assessment also addresses the issue of scaling. It is designed to place different health states on an interval scale. That is, a scale where each increment has the same meaning (just as each increment on a thermometer indicates the same increase in temperature). Thus, the purpose of utility assessment is to assign values to different health states on a common numerical scale that has meaningful intervals.

## Techniques for Utility Assessment

Several techniques have been developed to assess the utility of health states. [4-7] The simplest method is the Visual Analog Scale (VAS). The patient is presented with a visual numerical scale that ranges from 0 to 100. The endpoints are labeled perfect health (100) and immediate death (0). The patient is then asked to place each health state on the scale to reflect his or her preference for that state. Although the VAS is easy to present to patients and easy for them to answer, it has its limitations. Typically, patients are given very little guidance about what numbers to select. Thus, the visual analogue scale does not guarantee that the intervals on the scale are meaningful. Because of this limitation, utility theorists have turned to more complex methods of utility assessment.

A second utility assessment method is Time Trade Off (TTO). The patient is asked how much life expectancy he/she would forgo in order to move from a state of poor health to perfect health. This cascade of questions is continued until the patient's indifference point is established, i.e. the period of time in perfect health that is just as attractive as a longer time period with a specified side effect or

symptom. The utility of the symptom is then determined by dividing the indifference-point value by the period with the symptom. This approach is often used to adjust life expectancy for quality, resulting in a metric called quality-adjusted life expectancy.

In TTO, the utility of perfect health is 1.0 by definition and the utility of immediate death is 0.0, because immediate death is just as attractive as 0 years in perfect health. Thus to say a particular health state or symptom has a utility of 0.7 is to say that it is 70% of the way from immediate death to perfect health. TTO puts all health states on a common scale of the proportion of years of life one is willing to forgo. It assumes that all years of life are equally important. For example, it assumes that living from age 70 to age 80 is twice as important as living from age 70 to age 75. This assumption may not be accurate. Patients may value life years far in the future less than years in the near future. It also assumes that the sequence of various health states makes little difference. Another limitation of TTO is that it requires that patients be willing to trade off length of life and quality of life.

A third utility assessment technique is the Standard Gamble (SG). It asks patients to consider what risk of death they would accept in order to move from a state of poor health to perfect health. Depending on the patients answer, the complementary probabilities are adjusted and an additional choice is posed. This cascade of questions is continued until the patient's indifference point is determined. That is, the probability of death that makes the lottery just as attractive as the state of poor health for sure. The utility of a health state is computed as the probability of perfect health at the indifference point. Thus, if a patient said that a gamble giving a 70% chance of perfect health and a 30% risk of immediate death was just as attractive as a particular health state, then his/her utility for that health state would be 0.70. As with TTO, this utility can be compared to the utilities of perfect health (1.0) and immediate death (0.0). The utility of the other health states would be assessed similarly.

SG puts all health states on a common scale by comparing intermediate health states to a gamble between perfect health and death and finding the point at which they are psychologically equivalent. This technique assumes that each 1% increase in the risk of death is viewed the same. That is, increasing the risk from 0% to 1% is psychologically the same change as an increase from 20% to 21%. This assumption might not be accurate if patients distort some probabilities. There is some evidence that people generally overweight small probabilities and underweight larger ones. [8] Anther limitation of SG is that it requires an understanding of probability.

The time trade-off and standard gamble techniques share one important feature. They both require that the patient make choices between potential health states (or combinations of health states). The utility values obtained are the result of pairwise choices the patient has made. In contrast, the visual analogue scale merely asks patients to pick a number for each health state without making explicit choices. Because these scores are assessed to guide decisions, it is reasonable to think that basing them on explicit choices is a better indicator of the patient's true preferences.

## Research on Patient Utility Assessment

A number of studies have employed utility assessment to evaluate patients' preferences. Some have used cancer patients, while others have elicited preferences from other types of patients, healthy volunteers, or clinicians. This research has revealed several common results.

*Many Patients Are Reluctant to Make Trade Offs*

The Time Trade Off and Standard Gamble techniques require that the respondent makes a trade-off by accepting a shorter life expectancy or a risk of death in exchange for improved health. A number of studies have found, however, that patients are sometimes unwilling to make these trade-offs. At least 50% of patients with testicular or colorectal cancer who were asked to make TTO judgments were unwilling to trade-off any longevity for improved quality of health. [9] A similar result was obtained in a study of patients who were 6 months post-MI and who were asked to give a TTO evaluation of their own current health. Seventy-six percent of these patients refused to trade any time. Many of these patients viewed their current health as indistinguishable from perfect health, which explains their unwillingness to trade, but 10% of the patients refused to trade even though they described their health as less than perfect. [10]

Another study found many cancer patients unwilling to trade any time at all in the TTO, even though these same patients gave a less-than-perfect VAS score to the health state being evaluated. [11] This shows that their unwillingness to trade was not a result of patients not distinguishing the health state from perfect health. A similar result was obtained in a health status survey of community members in which a large number of the health states were evaluated with the TTO method. [12] The median TTO score was 1.0, indicating that over half the respondents were unwilling to give up any time at all. Results such as these have led some investigators to question the validity of TTO for assessing patients' preferences: "For people reluctant to say they will give up any life at all, questions that involve risking or trading life seem likely to be poor measures of the values of health states". [13]

Not all studies have shown such an extreme unwillingness to make trade-offs. A survey of a cohort of men, age 45-70, found that the majority were willing to choose a hypothetical treatment for prostate cancer that shortened life by 6 months (out of a 5 year interval) to maintain sexual functioning. [14] However, none of these patients actually had prostate cancer or were facing a choice between therapies.

*Different Assessment Techniques Lead to Different Utility Values*

TTO, SG, and VAS are all intended to measure patient preferences (although only the SG assesses utility in the strictest sense). However, there is usually some

variability in the scores each method assigns to a given health state. Different methods for valuing health states can produce different results.

For example, healthy adult and nursing home residents were asked to use TTO, SG, and VAS to evaluate six health states: perfect health, death, current health, coma, dementia, and constant pain. These states were selected to include one (coma) that was rated as equal to or worse than death by a majority of respondents. All three methods of assessment distinguished health states better and worse than death at the group level, but the different methods often did not rank order the health states identically. Only 7% of the nursing home residents and 42% of the healthy adults ranked the health states in the same order with the VAS and SG methods. Only 40% of both groups gave the same rank order with TTO and SG. [15] Differences among these three methods may account for the disagreements: VAS and TTO are risk-free in that they require judgments of certain health outcomes. In contrast, SG requires judgments of risky or probabilistic outcomes. In TTO, the duration of the health state is explicitly specified (e.g., 5, 10 or even 20 years), while in VAS and SG, duration is usually implicit (e.g., "for the rest of your life"). VAS asks for direct judgments of preference, while TTO and SG infer value, indirectly, by using a series of choices to calculate an indifference point. [15]

In another investigation, 87 psoriasis patients used VAS ratings, SG, and TTO to assess three health states that differed in disease severity and adverse outcomes of therapy. VAS ratings did not correlate well with TTO and SG utilities, although the latter two did not differ significantly from one another. [16]

In addition to weak correlation across methods, different methods give different average utility scores. Mean SG scores are usually higher than TTO scores, which are in turn higher than mean VAS ratings. For example, in a study of utility for two treatments (surgery or radiation) for laryngeal cancer, the TTO and SG utilities of former cancer patients, clinicians, and members of the general population were higher than VAS ratings for the same health states. [17] Another study [18] of this issue interviewed two groups of patients, 68 with testicular cancer and 100 with colorectal cancer. Mean TTO scores were higher than mean VAS ratings, but a power transformation of group mean VAS scores modeled group mean TTO utilities fairly well. The power function used [$VAS= 1 - (1 - TTO)^{0.64}$] is similar to one previously proposed by Torrance. [19] However, unlike Torrance's results, the fit was at the group mean level and did not work well for individual utilities. There was too much unexplained variation in the TTO scores for the VAS to be considered a reasonable substitute.

Differences between SG and TTO scores may be due to the fact that TTO utilities do not include attitude toward risk while SG utilities do. Therefore, different utilities for the same health states obtained by the two methods might be due to risk attitude. [20] To test this hypothesis, 30 patients who had been treated for testicular cancer assessed four relevant health states. Eighty-five percent of the patients were risk-averse, and SG utilities were on average higher than TTO scores. The investigators mathematically adjusted the TTO scores for risk attitude and found that adjusted TTO scores were higher than unadjusted scores and were not significantly different from SG utilities on 3 of 4 states, but they were slightly and

consistently lower. These results point to the importance of taking the risk attitude of the patient into consideration when making individual treatment decisions.

Because VAS is easier to administer, O'Leary, et al [11]investigated whether VAS could be used as a proxy for the TTO method. The participants were 124 cancer patients. TTO utilities tended to be somewhat higher than rating scale values, in part because many respondents who were willing to trade off any time at all gave rating scale values of less than 100. The mathematical relationship between the two measures was examined. A power function proved unsatisfactory, but a plateau relation captured the result that TTO scores were sometimes 1.0 even when VAS ratings were less than perfect.

*Utility May be Influenced by Experience with Disease*

In addition to effects of measurement method, utility scores are also influenced by the personal characteristics of the respondents. Perhaps the most important of these effects is that personal experience with a health state may influence its judged utility. In a landmark study [21] utilities were elicited for the health state of having a colostomy following treatment for carcinoma of the rectum. Patients with a colostomy gave that state a higher utility than healthy people or patients without a colostomy. This result suggests that utilities for a particular state may change when an individual enters that state and that patients adapt to intermediate health states more than they think they will. Similarly, TTO judgments elicited from women who had experienced breast cancer were different than those for women who had not. [22]

This result is not consistently replicated. Van der Donk, et al[17] found that patients gave lower utility scores than did clinicians and healthy volunteers for surgery and radiation treatments for laryngeal cancer. Thus, the effect of personal experience on utility judgments remains unclear.

Utility judgments from 66 laryngeal cancer patients were assessed both before and after a 4-week course of radiation therapy. [23] Patients gave TTO and rating scale judgments of three hypothetical health states (mild/moderate/severe treatment-induced effects). Because patients' health was expected to decline during therapy, the investigators predicted that patients' evaluation of their end-of-therapy health state would be more positive in the post-therapy assessment than in the pre-therapy assessment. The results, however, showed that utilities of the 3 hypothetical states did not differ in the before and after conditions, and that adaptation was limited or insignificant. Patients who showed a severe decline in voice quality during therapy, however, showed a trend in the predicted direction. These results suggest that simple exposure to a state of poor health may not necessarily change the subjective utility of that state. The limits of adaptation to poor health and the conditions affecting the degree of adaptation, as reflected in utility judgments, are still not well understood.

Experience is not the only personal characteristic to affect utility judgments. Age also affects the willingness of patients to make the trade-offs involved in TTO and

SG methods. [24,25] In one study [24] cancer patients of different ages considered scenarios about chemotherapy and chose between chemotherapy treatments with mild versus severe toxicity. The probability of l-year survival was varied for the two treatments. Younger patients (age less than 65) required a smaller gain in survival probability than older patients in order to switch to the more toxic treatment. In a second study, patients who had been treated for early-stage breast cancer were given hypothetical scenarios about treatment for metastatic breast cancer. The scenarios presented a choice of whether to undergo treatment with varying side effects and a 50% chance of an increase in life expectancy that varied from one week to 5 years. Younger patients were more willing to undergo severe side effects for a given benefit than were older patients(15). In both studies, younger patients will willing to accept more severe side effects for the sake of a modest gain in survival probability or life expectancy.

Again, these findings have not been consistently replicated. Older hip replacement patients and those less educated were more willing to trade away years of life for better health than were younger or college educated patients, even though the all patients had equivalent scores on a measure of clinical status, the Sickness Impact Profile. [26] A large study community survey used TTO to evaluate various health states. Older respondents were more willing to give up longevity for improved health. [27] Family and work responsibilities also affected trade-offs between length and quality of life in a study of cancer patients. [28] Finally, patients are likely to show higher utility for health states that include improvements particularly relevant to them. Hypothetical choices between surgery or watchful waiting for localized prostate cancer were given to l48 male patients in a general medicine clinic. [29] Surgery was described as having a 1-2% mortality risk. The expected survival benefit of surgery over watchful waiting was varied from 0 to 1 0 years. Preferences were influenced by the patient's own symptoms. Those with current urinary dribbling were more likely to prefer watchful waiting, while those with current difficulty starting urination were more likely to prefer surgery. Another interesting finding was that 43% of respondents preferred surgery even when it offered no long term survival benefit and had an immediate mortality risk, suggesting that patients have preferences for actions and not just for the health states that result from those actions. In addition, 24% of respondents were more likely to reject surgery as the long term survival benefit from surgery increased. This finding is ambiguous: If quality of life is disregarded, it is the opposite of what one would expect, because any level of surgical mortality risk should be more acceptable as it offers a greater long term survival benefit. On the other hand, these respondents may have thought the quality of life resulting from surgery was so poor they did not want it extended and that they were implicitly trading off quality vs. quantity. In using SG and TTO, care must be taken to word the questions to avoid such ambiguities and to insure that patients understand the questions.

*How to Overcome Difficulties in Utility Assessment*

This review indicates that utility judgments may have some troublesome properties. In particular, many patients seem unwilling to make the trade-offs required by the SG and TTO methods, and different methods give different utility values. How can these limitations be addressed?

Mathematical transformations have been used to address the issue of disagreements among the different methods. These efforts have been quite successful, although they cannot explain why different methods sometimes give different rank orders of health states.

The unwillingness of patients to make trade-offs is addressed in a recent study. [30] Two groups of prostate cancer patients evaluated three hypothetical health states using the TTO method. One group was asked to choose between living 10 years in a state of poor health or living a lesser amount of time in perfect health. About a third of all their TTO judgments showed a refusal to give up any longevity at all. A second group completed a modified task. They compared two hypothetical friends, one who would live in poor health for 10 years and another who would live in perfect health for less than 10 years. They decided which friend they would prefer to be. This form of questioning led to a much greater willingness to trade-off and greatly increased the number of patients who gave TTO assessments that ordered the three health states correctly. Thus, although utility assessment research has demonstrated some problems, current research has identified ways to gather valid utility data from patients.

*How to Incorporate Patient Preferences into the Final Decision*

How useful are utility judgments once they have been collected? How do they influence patient outcomes? Utilities can influence individual patient decision making and they can also influence health policy.

The effect of utility judgment on individual decision making is illustrated by a study of a decision aid that was tested with 30 healthy volunteers. The aid presents a decision about adjuvant chemotherapy. Several options are presented which differ in the resulting risk of recurrence and the toxicity of therapy. Thus respondents are asked to make trade-offs. Respondents shifted their preferences in predictable ways when changes were made in the reduction in risk of recurrence due to therapy and the toxicity of therapy. [31]

Utility judgments can also affect policy about how large groups of patients are treated. A decision analysis [2] on whether to screen for prostate cancer used TTO utilities provided by clinicians as inputs. The decision analysis showed that PSA screening increases survival, but decreases quality-adjusted life expectancy. Inclusion of the utility judgments changed the result from a recommendation to screen to a recommendation not to screen, indicating that utility judgments are crucial in making these sorts of medical decisions.

A similar decision analysis [32] used TTO utility judgments from 10 male patients without prostate cancer. The results were the same: when utilities for health states are taken in to account to estimate quality-adjusted life expectancy, no screening is the preferred strategy. Another decision analysis [33] of treatment strategies for breast cancer used utilities provided by expert oncologists.

These examples all illustrate that the strategy recommended by a decision analysis involving cancer frequently depends on the utilities used in the analysis. The analysis is "utility sensitive". However, none of these decision analyses employed judgments from patients who actually suffered from the disease, nor did they follow these patients longitudinally to assess the effect of experience with the disease and its consequences upon their utility judgments. Future research is needed on both patient utility assessment and decision analyses employing these utilities.

## Conclusion

Let us consider how this process works with a hypothetical patient. A patient is faced with a choice among treatments for a particular cancer. How would utility assessment help with this decision? According to decision theory, the patient should know the alternatives available to him/her. He/she should then be told about the relevant health states that could result from each of these options and provided with estimates of the likelihood of each outcome given each treatment option.

At this point, the patient is ready to employ utility assessment. Using one of the methods discussed (VAS, TTO, or SG), he/she should assign utilities to each of the relevant health states or side effects. Then an overall expected utility score for each treatment option can be computed by multiplying the utility of each health state or side effect by the probability or likelihood that it will occur, and summing over all the health states for a given treatment option. This strategy for making decisions combines the physician's knowledge of the treatment options and their probable effects with the patient's personal assessment of how good or bad each outcome would be for him/her. The treatment with the highest overall score from the patient is the option that should be selected because it is the alternative most in line with his/her own preferences.

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# COSTS AND COST-EFFECTIVENESS OF NEW TECHNOLOGIES IN CANCER

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## Why Cost-Effectiveness Analyses in Cancer?

The delivery of healthcare has changed significantly, from the perspective of both physicians and patients, in recent years. Previously, the physician was the advocate of the patient, and the insurer was only a distant, third-party observer who picked up the bill at the end. There were many advantages to this system of care: the patient received high quality care and could be relatively sure that his physician was doing everything possible for him, physicians were free to operate in a relatively independent manner which was professionally satisfying, and America was home to some of the most cutting-edge technologies in the world.

Unfortunately, our wealth of freedom and technology did not come without a hefty price tag. National health expenditures have risen to approximately $1 trillion or over 14% of gross domestic product. The real implications of this much-discussed dollar figure is that the cost of health insurance has become too high for many Americans (40 million uninsured in 1994).[1] Federal, state, and local governments struggle to control their ever-growing health care expenditures, and high premium costs are forcing employers to increase the price of the goods or services they sell, reduce the wages paid to employees, and/or scale back benefit packages offered.

Some have argued that we can't put a price tag on health. Why should 14% (or even 20%) of GDP be too much? We are an advanced and wealthy society that values health very highly. Perhaps this level of spending is appropriate. Arguably, "How much is enough?" is a question for our society to decide, not the health

economists. Unfortunately, that is not the end of this issue. The level of health care expenditures is not just about absolute dollar amounts. It is about what we are getting for those dollars. If there is one irreversible change in medical care as a result of our nation's fiscal crisis, it is the unwavering demand on the part of health care consumers (insurers, governments, employers, patients) to obtain value for their health care dollar. A new age of accountability has dawned and there is no turning back.

Cost effectiveness analysis is an important tool for demonstrating the value of a new treatment technology because it presents both the costs and the health outcomes (what we are really purchasing) of two or more alternatives. This chapter to will visit many of the issues which arise when conducting these types of analyses. Special attention will be given to conducting cost-effectiveness analyses for cancer treatments. This chapter concludes with a discussion of the importance of these analyses for the future of cancer care.

## What is a Cost-Effectiveness Study?

*Cost-effectiveness analysis* (CEA) is a type of analysis which is used to compare the costs and outcomes of two or more interventions or treatments. The result of this analysis is usually an incremental cost-effectiveness ratio (the dollars increase in cost per incremental gain in outcomes). Table 1 presents an example of a simple CEA analysis. [2]

**Table 1.** Example of a Cost-Effectiveness Analysis: Vinorelbine, Vinorelbine Plus Cisplatin, and Vindesine Plus Cisplatin for Non-Small-Cell Lung Cancer. [2]

| *Item* | *Cost* | *Incremental Cost* | *Incremental Outcome* | *C/E Ratio* |
|---|---|---|---|---|
| Vinorelbine | $10,000 | ---- | ---- | ---- |
| Vinorelbine + Cisplatin | $12,700 | $ 2,700 | 56 days | $17,100/ life year |
| Vinblastine + Cisplatin | $11,150 | $ 1,150 | 19 days | $22,100/ life year |

In the study results presented by Smith et al [2] and outlined in Table 1, two chemotherapeutic regimens are compared to "standard therapy" of Vinorelbine (NVB). The authors find that although both Vinorelbine plus Cisplatin

(NVB+CDDP) and Vinblastine plus Cisplatin (VLB + CDDP) cost more than NVB alone, they also result in longer survival (in days). By looking at the incremental cost of NVB+CDDP and VLB+CDDP relative to NVB alone ($2,700 and $1,150, respectively) and by calculating the incremental change in outcome (increase survival by 56 and 19 days respectively), the authors determine that NVB+CDDP is the most cost-effective regimen of the three. Note that although VLB + CDDP yields superior outcomes to NVB at a lower cost than NVB + CDDP, the cost per year of life saved is greater than NVB+CDDP and, therefore, it is less cost-effective.

*Cost minimization analysis* is conducted when the difference in outcomes between two treatments is presumed to be minimal. In this case, the treatments may be compared solely on the basis of cost. Table 2 presents an example of cost minimization analysis. [3]

**Table 2.** Example of a Cost Minimization Analysis: Allogeneic Peripheral Blood Versus Bone Marrow Transplantation for Hematologic Malignancies [3]

| *Cost Category* | *Allogeneic PBSCT (n=21)* | *Allogeneic BMT (n=14)* |
|---|---|---|
| Harvest | $4,980 | $4,332 |
| Pharmacy | $24,742 | $33,010 |
| Hospital Stay | $28,217 | $32,980 |
| Lab/Radiology | $5,688 | $7,840 |
| Blood Bank | $13,925 | $13,351 |
| Outpatient | $18,391 | $18,481 |
| Other | $4,599 | $4,868 |
| Total | $100,542 | $114,862 |

Costs of allogeneic peripheral blood stem cell transplant (AlloPBSCT) and allogeneic bone marrow transplant (AlloBMT) are compared for a small group of patients. Because of the relatively novel nature of AlloPBSCT at the time of this study, a sizable clinical trial which could establish efficacy (i.e. differences in outcomes) of the two treatments had not yet been conducted. An analysis of medical costs, however, can be conducted, keeping in mind the non-random nature of the patient assignment. Many cost minimization studies choose to focus on the components of costs. As Table 2 illustrates, this type of breakdown can provide meaningful information for transplant coordinators, clinicians and policy makers.

*Cost-benefit analysis* does consider both costs and outcomes, but is different from CEA in that the researcher is required to assign dollar values to the benefits of

the treatments. The cost-benefit ratio, then, is the ratio of the dollar costs to the dollar benefits of the treatment in question. Table 3 presents an example of a cost-benefit analysis. [4]

**Table 3.** Example of a Cost-Benefit Analysis: Mandatory Premarital Testing for HIV. [4]

| | | | | *Benefit-Cost Ratio* | |
|---|---|---|---|---|---|
| *True Positive Tests* | *HIV Cases Resulting in AIDS* | *Cases of HIV Prevented* | *Cases of AIDS Prevented* | *Program Cost = $35 Million* | *Program Cost =$170 Million* |
| | | | | *Value of Life* | *= $400,000* |
| 2,600 | 0.75 | 357 | 268 | 3.1 | 0.6 |
| | 0.99 | 357 | 353 | 4.0 | 0.8 |
| 9,700 | 0.75 | 1,334 | 1,000 | 11.4 | 2.4 |
| | 0.99 | 1,334 | 1,320 | 15.1 | 3.1* |
| | | | | *Value of Life* | *=$2,000,000* |
| 2,600 | 0.75 | 357 | 268 | 15.3 | 3.2 |
| | 0.99 | 357 | 353 | 20.2 | 4.2 |
| 9,700 | 0.75 | 1,334 | 1,000 | 57.2 | 11.8 |
| | 0.99 | 1,334 | 1,320 | 75.5 | 15.5* |

Assumptions:
1. 75% Premarital sex
2. 50% Safe sex
3. Transmission rates: 10% premarital, 35% overall

*Believed by authors to be most likely scenarios.

Because cost-benefit analyses are usually reserved for policy-level evaluations, most of the literature in this area focuses on disease screening. The example shown in Table 3, while not specifically a cancer example, is particularly noteworthy because it demonstrates the sensitivity of results to underlying assumptions about transmission and precaution rates, sensitivity and specificity of testing, and the value of life. The result of a cost-benefit analysis will be the benefit-to-cost ratio. Obviously, this ratio should exceed 1. However, not every program whose benefit-to-cost ratio exceeds 1 will necessarily be funded. As with any undertaking, there

are competing uses for limited funds. From a policy perspective, various programs should be ranked by their respective benefit-to-cost ratios and the money set aside for these programs should be spent on the "top contenders" on the list. Alternatively, if cost-benefit evaluations of programs are not available contemporaneously, a historically acceptable level of benefit-to-cost ratios (e.g. greater than 10) may be established to determine fundability of programs as evaluations become available. This type of approach has evolved for cost-effectiveness analyses, where the "acceptable" range of cost-effectiveness (CE) ratio is somewhere between $40,000 and $60,000—interventions whose CE ratio is above $60,000 (dollars per life year or dollars per quality-adjusted life year) are generally not considered to be cost effective.

## What are Costs?

Measuring costs is not often a simple or straightforward task. Issues of which costs should be measured as well as the more difficult question of how to measure the actual cost of each item must be addressed . The following discussion describes the main issues which must be decided before conducting a cost analysis. For some issues, there is a relatively clear consensus on the best approach; for others a controversy still exists. We will provide short discussions of these issues. One particularly helpful resource is the recently published work of the Panel on Cost-Effectiveness in Health and Medicine. [5-8] These works represent a consensus of field leaders, convened by the US Public Health Service, providing detailed guidelines for the conduct of studies as well as the format for presentation. Given the high profile nature of this work and these publications, it is likely that these guidelines will set the standard for work in the area of cost analyses.

*Perspective of the Analysis*

The perspective of a cost analysis determines the relevant costs to consider. For example, when thinking about the costs of various types of cancer treatment, one could consider the costs from the perspective of the patient, the employer, the provider (e.g. hospital or physician), the insurance company, the government, or society. Each of these perspectives has different sets of relevant costs. Table 4 outlines the costs that might be relevant to each of these players and demonstrates how these costs can differ significantly.

General consensus in the economic literature favors utilizing the societal perspective when conducting cost analyses. The advantage of conducting the cost analysis from the perspective of society is that takes into account all of the costs stemming from the treatment choice. This is especially important when the cost savings which accrue to one member of society as a result of employing one type of treatment impose costs on another member of society. For example, getting a patient out of the hospital more quickly may significantly reduce the costs faced by an insurer, but this type of treatment also imposes significant costs on the patient

and his or her caregiver. Conducting a cost analysis from a societal perspective allows a researcher to explicitly consider these tradeoffs. This perspective is advocated by the Panel on Cost-Effectiveness in Health and Medicine. [5]

**Table 4.** Examples of Different Perspectives for Analysis and Relevant Costs.

| *Payer* | *Relevant Costs* |
|---|---|
| Patient | Health insurance copayments, lost work time, travel costs to the physician(s), hospital(s) and clinic(s). |
| Provider | Cost of providing a particular treatment, including labor, materials, and overhead costs |
| Employer | Increased health insurance premiums, lost employee productivity |
| Insurance Company | Payments for physican visits, hospital stay, hospice, pharmaceuticeals, home health, rehabilitation |
| Government | Medicaid & Medicare, includes same costs as insurance compay; also includes the cost of mental health care, social support services, and the criminal justice system (which may be associated with the treatment of particular diseases) |
| Society | Total of costs to patients, employers, providers and all other members of society |

*Types of Costs Included in the Analysis*

Costs associated with a treatment or intervention are usually broken into three main categories: direct medical costs, direct non-medical costs, and indirect costs. Gold et al further disaggregate costs by dividing indirect costs into (patient) time costs and productivity costs. [8]

*Direct medical costs* include all costs associated with the treatment; costs of hospital stays, physician visits, laboratory testing, pharmaceuticals, and home health care are examples of direct medical costs. There is very little disagreement in the literature that these costs should be included in all cost analyses.

*Direct non-medical costs* include those costs directly associated with treatment which are non-medical in nature; transportation and parking costs or the cost of special meals are examples of direct non-medical costs. While most researchers quickly acknowledge the relevance of these costs, relatively few cost analyses contain these direct non-medical costs because the data is not often collected. Gold et al point out that omission of these costs may lead to significant biases in results. [8] Direct non-medical costs should only be omitted is there is strong a priori evidence that these costs are not likely to differ across arms of the study.

*Indirect costs* include those costs which are not directly attributable to the treatment but may be the result of the condition or the treatment. Work time lost by patient and caregiver and productivity losses due to morbidity are examples of indirect costs. Because indirect costs are also reflected in differences in utility of various health states, researchers must be careful not to "double count" indirect costs. The inclusion of indirect costs in the numerator (i.e. as a financial cost) rather than the denominator (i.e. as a difference in quality-adjusted life years) of the cost-effectiveness ratio is the subject of significant controversy. Gold et al present strong arguments supporting the inclusion of indirect costs in the denominator (i.e. as differences in patient utility for the various health states).[8] This approach avoids the somewhat subjective assignment of dollar values to these types of costs and explicitly considers patient valuation of these costs.

*Methods of Direct Cost Data Collection*

Techniques for the collection of health resource utilization vary widely in cost analyses. Cost analyses associated with randomized controlled trials (RCTs) typically include extensive primary data collection during the course of treatment (i.e. research assistants filling in data forms based on patient chart information and physician query). The shortcoming of this approach is that researchers are unable to track utilization beyond the initial treatment period. In addition, many researchers and clinicians complain that the protocols associated with RCTs depart significantly from community practice and, therefore, do not provide "real world" costs. Finally, this method of data collection can be cumbersome and expensive to complete.

Secondary data are often a less expensive form of data and usually provide better longitudinal "real world" data than a typical RCT. Examples of this type of data collection include use of administrative (billing) databases or use of insurer (claims) databases. Unfortunately, analysis of this type of data must contend with potential selection bias problems due to non-random assignment of patients to treatment groups.

A third method of data collection, patient diary, is sometimes used to supplement other collection efforts. The major obstacle associated with this type of data

collection is the problem of accurate patient recall. There is some evidence, however, that patient recall accuracy is relatively high, with measures of agreement (kappa) between patient report and medical chart as high as 88 to 96 %. [9-14] While recall appears to deteriorate rapidly after 10 months, it appears to be relatively stable for periods of up to three months. [9,14]

Gold et al acknowledge the advantages and disadvantages of each of these three methods of data collection and seem to advocate the approach or combination of approaches which most "cost effectively" provides sufficient, accurate, and unbiased data. [8] In the interest of "cost effectiveness" of data collection efforts, a number of researchers are turning to existing administrative databases such as the hospital or physician practice billing database or Medicare claims data (for the over-65 population) to provide information. [15,16]

*Estimating Costs*

When assigning costs to "cost out" the resource utilization captured through data collection efforts, it is desirable to capture the real cost to society of the treatment by identifying its "opportunity cost" or the value of the resources in their next best alternative. While market prices are generally presumed to reflect opportunity costs to society, true prices are more difficult to observe in the health care market, and they may be subject to market distortions (such as insurance). In this case, it is usually desirable to adjust prices to more accurately reflect costs.

One of the most common methods of adjusting prices, especially for inpatient data, is to multiply charges by ratio(s) of cost-to-charges (RCCs) based on hospital-wide or department-specific data. This method was employed extensively by the AHCPR-funded Patient Outcome Research Teams (PORTs). [16] Because RCC data is not typically available outside the inpatient setting, researchers estimating costs of physician visits and other non-inpatient medical care have generally relied on prices or some standardized set of costs. Recent (full) phase-in of the new Medicare Fee Schedule based on the Resource Based Relative Value Scale (RBRVS) presents researchers with a common metric for costing out physician (and other professional) services. [8]

*Discounting*

Because costs of treatment can be incurred over a relatively long period of time, especially when considering the costs of cancer recurrence, it has become standard in economic analyses to discount costs to a "base year" whenever costs are incurred over more than one year. This base year is often the first or the last year of the study. While there is no strong theoretical reason for selecting a particular year, a number of researchers favor use of the final year because the cost estimates are expressed in dollars similar to the current year. This adjustment of costs specifically acknowledges society's rate of time preference. In calculating the costs of a treatment, researchers must take into account the fact that incurring an expense

of $100 today is not the same as incurring that cost one year from now; society would rather incur that cost one year from now. If society is indifferent between incurring a cost of $100 today and incurring a cost of $103 one year from now, the rate of time preference is 3 %; this 3 % figure should be used to discount all future costs to the present when comparing costs of two or more treatments. This time preference adjustment is especially important when treatments differ in the stream of costs. Discounting should not be confused with inflation adjustments which account for changes in purchasing power. These adjustments should also be conducted to provide consistent cost estimates. Although there is little theoretical basis for the selection of any particular rate of time preference, Weinstein et al recommend the use of both 3% and 5% because 1) evidence on the real (inflation-adjusted) interest rate indicates that society's rate of time preference falls in this range, and 2) use of these values will enhance comparability of cost-effectiveness study findings. [2]

## What are Outcomes?

Unless the interventions or procedures being compared in the cost-effectiveness analysis are expected to yield identical outcomes, it is important to measure the impact of these interventions on health outcome(s). One of the most common measures of health outcome is mortality/survival. Many CEA studies, especially those conducted during the early years of health services research, express CEA ratios as *cost per year of life saved* (or, when comparing 2 interventions, incremental cost per incremental year of life saved). Table 1 provided an example of a cost-effectiveness analysis using years of life saved as the denominator in the CEA ratio.

Many researchers have noted, however, that years of life saved may not be the only relevant health outcome. Interventions or procedures may have a substantial effect on patient ability to see, hear, eat, sleep, ambulate, socialize, and/or work. In short, it is not always enough to look out how long a patient will live; researchers must also evaluate the "quality" of those years. Using various methods to measure the quality of life in each type of "health state", weighting schema can be developed which attach a value to a year of life in each state. For example, in-depth interviews to determine preferences may reveal that, on average, a year of life with impotence (due to treatment for prostate cancer) is equivalent in value to 6 months of life in perfect health. The weights in this simple example would be: 1.0 for each year in perfect health; 0.5 for each year of impotence. Table 5 illustrates how these weights would be combined with cost and life expectancy information to develop CEA measures.

Even though Drug B increases the patient's life expectancy by 2 years (relative to Drug A), CEA reveals that because Drug B results in a very high rate of impotency and because impotency significantly reduces quality of life, Drug B is not found to be cost-effective.

Other types of outcomes have been used in cost-effectiveness analyses, although they are less common than life years or quality-adjusted life years (QALYs). For example, when examining the cost effectiveness of growth factor use during chemotherapy regimes, clinical studies may examine the number of infection days or neutropenic days associated with the treatment versus control arms of the study. Although this information on side effects can be combined into one outcome measure (the quality-adjusted portion of QALYs), in some cases it may be more clinically meaningful to present the data in a disaggregated format. In this case, the researcher may wish to present the cost-effectiveness ratio(s) of cost per infection day avoided (treatment relative to control) or cost per neutropenic day avoided. While there are fewer suitable benchmarks for this type of analysis, clinicians may find this information helpful.

**Table 5.** CEA of Two Hypothetical Prostate Cancer Treatment Drugs.

| *Item* | *Drug A* | *Drug B* |
|---|---|---|
| Life expectancy of 65 year old | 5.0 | 7.0 |
| Probability of impotency | 20% | 0% |
| "Expected Value" of 1 year of life* | 0.90 | 0.55 |
| Quality Adjusted Life Years (QALY) | 4.5 | 3.85 |
| Costs** | $10,000 | $10,000 |
| Cost per QALY | $2,222 | $2,597 |

*Using weighting scheme: year of perfect health = 1.0, year of impotency = 0.5. Expected value of one year of life = (Prob of Perfect Health)(1.0) + (Prob of Impotency)(0.5).

** The sum of all relevant costs

## When Should Cost-Effectiveness Analyses Be Used?

As discussed earlier, cost-effectiveness analyses are those analyses which combine both the costs and the outcomes of a specific intervention and its alternatives into a single measure or set of measures (usually cost per life year or cost per quality-adjusted life year). Cost effectiveness analysis should be used when there is reason to believe that both the costs (including *all* relevant costs) and the outcomes of specific intervention will differ from relevant alternatives. If the outcomes are not expected to differ significantly, the researcher may wish to consider a cost minimization analysis. On the other hand, if the costs are not expected to differ but the outcomes may be different, an efficacy study would be most helpful.

Cost effectiveness analyses are generally suitable for evaluation of new technologies relative to their closest alternative. When considering the costs and effectiveness of new program or policy change (as opposed to a focused intervention), however, researchers may wish to consider conducting a cost-benefit analysis. This type of analysis explicitly considers the value of the benefits (outcomes), instead of expressing these benefits/outcomes in life years or QALYs. The example given in this chapter (Table 3) looks at the costs and benefits of mandatory premarital screening for HIV. Life years saved are valued at $400,000 /year (alternatively $2,000,000/year) in order to develop benefit-cost ratios.

Although clinical science is still very focused on efficacy, it is becoming very clear that studies which totally ignore issues of cost may make the interventions they are studying "less competitive" when it comes to getting third-party payer reimbursement. The number of insurance companies, federal, state, and local agencies, managed care organizations, employers, and employer coalitions who are demanding accountability in health outcomes and costs will only grow. Cancer researchers can take steps to understand cost analyses and encourage companion economic studies in their efficacy research, or they can ignore the overwhelming waves of change and watch as finance-oriented administrators conduct analyses in significantly less clinically informed ways. Cost and outcome accountability is not a passing fad. If clinicians recognize the importance of cost effectiveness studies, they can maintain their control of the academic and clinical integrity of the studies and ensure that responsible decisions regarding the development and use of new technologies.

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# EVALUATING CANCER COSTS IN NCI TRIALS

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## Introduction

Historically, the evaluation of new, therapeutic strategies for cancer have depended exclusively on safety and clinical efficacy.[1] Today, there is an increasing recognition by health care providers and financing organizations of the resource constraints on the provision of these services, lending greater importance to their economic evaluation.[1-4] Further, as costs for such services continue to rise, there is also a heightened desire for information on the value for each dollar spent in providing these technologies.

Understanding the growing need for such information, the National Cancer Institute (NCI) held an economic conference in May of 1994 to discuss the integration of economic outcome measures into NCI-sponsored clinical trials.[5] The American Society of Clinical Oncology (ASCO) followed with establishment of a Health Economics Working Group established to develop guidelines and procedures for performing these analyses. This work led to the NCI/ASCO economic workshop in May of 1996. This workshop outlined procedures and guidelines for performing economic evaluations alongside cancer clinical trials in the form of a workbook.[6]

As a result of these efforts, the techniques born out of the field of clinical economics are currently being developed and applied to appropriately evaluate cancer costs in NCI-sponsored clinical trials. These methods take into account not only the costs of a new therapy, but its overall economic and clinical impact.[7]

This chapter briefly discusses these techniques in performing prospective economic evaluations in NCI clinical trials. To illustrate these techniques, the methodology of a recently completed prospective economic evaluation of a new cytokine therapy is described.

## Economic Analysis of Cancer Clinical Trials

Economic evaluation is concerned with the use of resources by patients within the clinical protocol. An economic evaluation deals with some of the same issues addressed by the clinical investigators, such as whether or not the patient received an MRI scan; however, for the clinical protocol the results of the MRI scan are important, while for the economic protocol the number of MRI scans consumed during the study period is the question of interest. While measures of resource quantities are important as clinical endpoints, or as descriptive measures, interpretation of charges in resource quantities may require further analysis. For example, a specific therapy may be shown to reduce length of stay for patients receiving bone marrow transplant, but may increase their need for follow-up physician visits on an outpatient basis. Thus, the patient will consume fewer days of inpatient care and more outpatient resources. One cannot determine a *priori* if the program is beneficial from this assessment. Costs are applied to resource utilization measures to allow an overall economic assessment of the change that has occurred as a result of treatment. For example, if inpatient days cost $700 each and physician visits cost $100 each, a therapy that costs $100 would save money if it reduced a hospital stay by one day but increased outpatient resource use up to an equivalent of six physician visits.

As illustrated in the preceding paragraph, there are several steps that are required in the development of an economic analysis plan for a clinical protocol:

1. Determine the resource quantities that will be collected for the purposes of the economic evaluation.

2. Determine a strategy for collecting those resources

3. Determine a strategy for collecting the costs of those resources.

4. Aggregate the cost and resource utilization as described in an economic analysis plan.

Developing economic data as end points in a clinical trial requires careful consideration and planning which should begin at the same time the clinical trial is being designed.[22] While there has recently been an increase in the number of clinical trials that are collecting economic data, the challenge remains to ensure that

clinical economic end points are considered early in the clinical development process. Table 1 outlines the subsequent steps in constructing the economic arm of a clinical trial. The initial step is to construct a plan that describes the overall economic study design. This requires the establishment of a set of economic end points for study (direct, indirect, or intangible costs), and development of a method for collecting these data. The strategy for data collection can be either retrospective or prospective. Although there are advantages and disadvantages to both types of data collection (Table 2), prospective collection of economic data is generally preferred.[6]

**Table 1.** Steps in Planning for an Economic Evaluation in Conjunction with a Clinical Trial. [8]

| *Step* | *Contributors* |
|---|---|
| Develop Economic Plan | EST, PI, PL |
| Design Data Collection Strategy | EST, PI, SC, PL, TM |
| Design Case Report Forms (CRF's) | CRF Designer, EST |
| Pilot-Test CRF's | PM, SC |
| Prepare Written Guidelines for CRF Completion | PM, EST |
| Train Investigators | PM, EST |
| Design Database | Data Management Personnel, EST |
| Develop a Source Document Verification Plan | PM, EST |
| Design Patient Release Forms | PM, EST |
| Design Record Log Sheets for Patient Self-Report Data | PM, EST |

EST = Economic Study Team; PI = Principal Investigators; PL = Project Leader; PM = Project Monitor; SC = Site Coordinators; TM = Trial Monitors. Adapted with permission from Mauskopf J, Schulman K, Bell L, et al. A strategy for collecting pharmacoeconomic data during phase II/III clinical trials. Pharmacoeconomics 1996, 9(3):264-77.

**Table 2.** Prospective Data Collection: Advantages and Disadvantages. [6]

| *Advantages* | *Disadvantages* |
|---|---|
| Information about key data elements, including demographic information, quality of life, and out-of-pocket medical costs is easily collected | May require more resources than simple analyses of administrative data sets |
| Can capture information about important resources used by patients that is not chronicled in the medical chart and can only be provided by the patient | Requires additional time for data collection effort |
| Can identify resource utilization *a priori for* easy prospective collection | Requires long lead time until data is available |
| Economic data are available when clinical data collection is completed | |

Other aspects of the economic study are to review the clinical protocol to ensure that there are no economic biases in the structure of the clinical trial (e.g., there are no fixed discharge criteria included in the study, and/or there are no differences in prescribed treatments across study arms). Where possible, the clinical protocol should be modified to reduce protocol-mandated tests or procedures in order to reduce protocol-induced changes in medical care (protocol induced costs or benefits) and to help ensure that the protocol mirrors "usual care" as much as possible. The time horizon for most cancer studies usually reflects other similar studies. However, the appropriate time horizon for new types of treatments may require further consideration.[9]

Unfortunately, most clinical trials are for a limited amount of time. Economic analysis is often interested in a long-term assessment of the impact of cancer therapies on a patient, usually throughout the patient's lifetime.[10] Therefore, economic analyses often evaluate results over two time periods: the study duration and the patient's lifetime. The time horizon for an economic evaluation of a cancer therapy is often different than that of the clinical trial. The optimal time horizon for the economic arm of the trial is to follow subjects from the time of randomization to

death [6]. Obviously, this can almost never be achieved. Economic evaluation has, instead, developed projection techniques using economic models. Based upon the effect of the results during the study period, various models are used to project these effects over a patient's lifetime. Both conservative (one-time-effect) and optimistic (continuous effect) models for assessment have been proposed to carry out these analyses.[11]

Finally, economic analysis is concerned with the generalizability of data developed from clinical trials. The external validity of studies is thus an important consideration in recruitment of subjects to the study. [12]

*Resource Measures*

Prior to the initiation of an economic study, the investigators must determine which data items to collect in the economic evaluation. These items should include both high-cost and high-frequency items, as well as items that will be affected by treatment.[13] Some economic evaluation strategies actually omit measurement of resource consumption and concentrate instead on economic measures of resource use, such as collection of hospital bills. Often this strategy raises the potential that differences measured across treatment arms merely reflect price differences rather than differences in resource consumption. However, collecting resource consumption measures may not be feasible at times or may be prohibitively expensive forcing the investigator to choose the alternative "billing" approach. Also, as will be discussed later, it may be difficult to develop specific costs for the resource quantities collected in the protocol.

Data on resource measures can be collected from medical records, medical bills, and patient self-report (Table 3). The appropriate source of information is dependent upon the type of resource information needed (e.g., direct medical costs, direct nonmedical costs, indirect medical costs, etc.). Data on resource use for direct medical costs can be collected based on the actual resources used to provide care. This may be done by patient interview, by review of patients' medical records (charts), by extraction from the hospital cost/billing systems, or with the use of managed care/insurer claims, when available. Data on resource use for indirect medical costs, intangible costs, and direct nonmedical costs can be collected through interview with the patients themselves or a caregiver. Specific resource use items that may be of interest to investigators are included in Table 4. Data on direct medical costs may only be available from the patient. Data on indirect morbidity costs (lost work days) may be available from the patient's employer or from patient self-report.

*Costs of Resources*

Financial information on resource use by patients may be available from the sources of care for the individual patient, or may be available on a systematic basis from an administrative data set. For example, most hospitals have administrative billing systems that can be used to assess the costs of resources consumed by

patients during a hospitalization. However, hospital billing information will only include a record of the specific services supplied by the hospital and may not include the cost of physician services during the hospital period. Except in specific settings, hospital billing information will not include information on the care received by the patient on an outpatient basis. Thus, if a protocol follows patients over an extended period of time, data collection mechanisms will need to be available to collect both inpatient and outpatient resource use as well as the cost of these resources.

**Table 3.** Sources of Economic Information. [6]

| *Resource Information* | *Source* |
|---|---|
| Direct Medical Costs | |
| Inpatient | Chart review (quantities or resources used), hospital cost accounting system, hospital billing system, managed care/insurer claims, patients |
| Outpatient | Chart review, practice billing systems (either at the physician level, or at the medical group or physician hospital organization level), managed care/insurer claims data, patients |
| Pharmacy | Chart review, patients, managed care/insurer, claims data, pharmaceutical benefits managers |
| Indirect Medical Costs | Patients (lost work days), caregivers, employee data |
| Intangible Costs | Patients |
| Direct Nonmedical Costs | Patients |

Administrative data bases, such as the claims payment records of a managed care organization for a large health plan, are becoming an increasingly important means of tracking resource use by patients in clinical protocols. However, given the fragmented nature of the health insurance system of the United States, the use of administrative data sets is not a feasible means of tracking resource use by study

patients unless the study is designed around specific patient populations such as patients over 65 (Medicare), or patients enrolled in a specific health plan (for example, the Kaiser Permanente Health Plan).

The main disadvantage of medical bills is that they are not available outside the US. Even in the US, capitated health care plans do not bill for individual services, and therefore may not be able to generate bills that can be used as the primary source of resource use information. In these cases, specific costing exercises may need to be undertaken using time-motion studies or other cost accounting methodologies.[14]

**Table 4.** Resource Use Data Items. [6]

| *Resource Use* | *Items Contained on CRF* |
|---|---|
| Inpatient at study hospital | Admit date, reason for admission, hospital room type, surgical oncology procedures, laboratory tests, radiologic tests, medications/ chemotherapy, radiotherapy, oncologist visits, date of discharge/death |
| Outpatient at study hospital | Date, type, and duration of visit, reason for visit, procedure, laboratory tests, radiologic tests, medications/ chemotherapy, radiotherapy, home care |
| Nonstudy site | Oncologist visits, emergency room visits, hospitalizations, nursing home, hospice, medications/chemotherapy |
| Outpatient at non-study site | Oncologist visits, emergency room visits, hospitalizations, nursing home, hospice,medications/chemotherapy |
| Patient resource use | Caregiver burden, days of usual activity, out-of-pocket expenses (e.g. lodging expenses to receive cancer care at a referral center), transportation costs (for oncologist visits, chemotherapy, radiation therapy, etc.) |

*Hospital Costs*

Hospital financial information is available in the form of hospital charges. Hospital charges are generally not thought to be a reflection of true costs of providing specific services to patients. Since economic evaluation is interested in the costs of providing services to patients, separate analysis of these data will need to be undertaken. Either one of two steps can be used to address this issue: 1) develop cost data based on hospital charges, or 2) develop cost data from a cost accounting system.

Hospitals in the United States must report their overall costs and their overall charges to the Health Care Financing Administration (HCFA) on an annual basis. This Medicare "cost report" has been used by investigators to develop a "cost-to-charge ratio" that is used to convert hospital charges to hospital costs for economic analysis.[15] These cost-to-charge ratios can be developed at either an aggregate level for the institution, or on a more specific level based on the different hospital departments providing services to patients (called UB-92 categories). The Uniform Bill-92 was developed and approved for use in 1992 to standardize billing practices for submission of claims to Medicare.[16] It contains provider and patient information; condition, occurrence, and value codes; revenue descriptions, codes, and charges; payer, insurer, and employer information; and diagnosis and procedure codes.

The relationship between costs and charges at hospitals actually varies considerably between hospital departments. Where possible, departmental (UB-92 level) cost-to-charge ratios may be a better proxy for costs of specific services than total hospital cost-to-charge ratios. One severe limitation to this more detailed approach to assessment of hospital costs is that each hospital may have their own system of assigning departments to UB-92 categories. Thus fresh frozen plasma may be included in the blood bank cost center report in one institution, but in the operating room cost center in a different institution. These differences may make it unfeasible to aggregate departmental cost-to-charge ratios in assessing hospital costs across institutions. One study has been developed by the Cancer and Leukemia Group B (CALGB) (CALGB-9570) that is designed to assess the capabilities of administrative data sets within CALGB member institutions. It is expected to come up with recommendations for strategies of requesting cost information from CALGB member institutions for economic evaluation of CALGB group studies.

Given the increasing financial pressures resulting from changes in the health care system, many hospitals have developed their own separate cost accounting systems to provide more detailed cost information for management decisions. However, not every institution has such an accounting system in place. Where these data sets exist, they can be used to assess the costs of services, and may be a better reflection of the cost of services than costs developed using a cost-to-charge ratio.

It is often difficult to develop costs for specific services from detailed hospital bills. Hospitals often keep track of every service received by an individual patient

on a disaggregated basis. Thus, for a specific procedure or treatment, for example, an intensive care unit day or an hour of operating room time, the hospital may bill for each of the hundreds of different components of that service separately. In fact, it may be impossible to develop an overall cost for specific services across institutions. One approach to resolving this issue is to develop a regression based model that will use the resource counts in the economic protocol as predictor variables in assessing the overall hospital bill. This technique could result in the development of bundled costs for the specific clinical services assessed in a case report form.[17]

*Other Costs*

Physicians assign common procedural terminology codes (CPT-4 codes) when billing for their services. In a manner analogous to hospitals, physicians have charges for specific services that may not be directly related to the costs of providing services. However, there is no physician cost-to-charge ratio. In 1992, HCFA developed the Resource Based Relative Value Scale (RBRVS) as a measure of the resource intensity of the specific physician services for each CPT-4 code. The Medicare system currently implements this resource intensity measure in physician payment.[15,18] Workload units called relative values (RVU's) may be used to calculate standard costs for physician services.[13,19]

Pharmaceutical charges also vary depending on the pharmacy. One way of standardizing pharmaceutical costs is to use the average wholesale price available for specific pharmaceutical products.[20]

Indirect costs of medical care can also be assessed directly within clinical trials. It is relatively easy to track work-loss or activity loss on a daily basis for patients in clinical trials. However, the evaluation of this work-loss may be problematic. For example, one means of evaluating the cost of loss per activity would be to assess the average income of patients in a clinical trial and use this measure of average daily wage of patients in the study as a measure of value for the work-loss. However, to the extent that clinical trials recruit unrepresentative populations from a socioeconomic perspective, this measure may be difficult to interpret. Further, this measure does not adequately value services for nonsalaried patients such as homemakers or students. An alternative approach is to apply national average daily wage as a measure of loss of productivity in these assessments.

*Economic Data Collection*

The data collection strategy for economic assessment of cancer therapies depends upon the resources available for data collection, the importance of validity-checking of specific data items, and the frequency of expected resource utilization. Since patients may use resources outside the study center, the patient is often the only person who knows the resources required for their treatment.[13] The data collection procedure often involves two steps, querying the patient to assess their use of medical resources, then source document checking of critical resources (i.e.,

data elements which serve as a primary study endpoint-either clinical or economic, or data elements which have a high degree of complexity such as hospitalizations). This strategy enables data to be collected for all medical care received by patients, whether or not it is provided at the study site. Further, it may report the level of use of medical care services (e.g. number of hospital days, physician visits, and major outpatient procedures since the last protocol visit). Patient self-report may substitute for data abstraction from medical records; however, it should not be substituted for medical records abstraction when very detailed data on medical care use are required (investigators will need to determine the extent of source document checking for economic data based on the importance of each data item and the costs of the source-document validation exercise).

In addition to direct medical resource use data, patient self-report may include assessment of the amount of care-giver time required for their care at home, and the number of days lost from work or other activities. Alternatively, work-loss could also be abstracted directly from a patient's work records, but it is unlikely that this would be feasible in a typical clinical trial unless the trial was restricted to patients with a single employer.

There are several different ways of collecting patient self-report data for resource use items. Patients may be interviewed, either at a protocol visit or over the telephone about their resource use. Alternatively, specially designed questionnaires may be mailed to them at regular intervals. Within the NCI cooperative group mechanism, it has been proposed that economic assessment be integrated with the regular clinical assessment already occurring through study coordinators.[6] This would entail modifying current data flow sheets to capture quantities of resource use in a more specific fashion than occurs currently.

Problems occur with patient self report data for a number of reasons. Patient recall of events becomes problematic when: (i) the recall period is extended (>2-3 months) [21], (ii) the patient is a high user of medical care services; and (iii) illness interferes with the patient's mental status. Thus, scheduled visits or telephone or mail contacts need to be sufficiently frequent to avoid recall problems. An alternative way to avoid recall problems is to ask the patient to complete a diary at home as care is received. The diary should then be brought to the study site at each visit, used by the patient as a reference during a telephone follow-up, or used as a reference when they complete the mail questionnaire. Potential problems with a diary are that patients may forget to complete them and/or not have them available when reporting the data. However, diary problems can be minimized through reminder telephone calls to the patient at regular intervals between visits to remind them to complete the diary, and by means of a letter sent before their next study visit, reminding them to bring in the diary. If the patients in the trial are not mentally competent, then the resource use items may need to be obtained from a proxy such as a family member or a close friend,

When collecting data centered around actual resource use, the case-report-forms (CRF's) used to collect the data must be designed and pilot tested prior to data collection. They should allow the investigators to record core areas of resource use

required for the study. Data can be collected regarding the resource use during the inpatient time period of the protocol, resource use during the outpatient period of the protocol, the resource use at any non-study site, and patient resource use. Table 4 depicts specific items that may be contained on the CRF's to capture the use of these resources.

*Confidentiality*

Economic evaluation may involve abstraction, by trial personnel, of data from the patient's medical records or medical bills. Billing information has a clear advantage as a source of resource utilization, in that bills are generally typed and include a clear listing of all the medical care use that generates a service charge. To obtain a patient's medical bill in the US, the principal investigator will need to include a release of information in the patient consent to obtain billing information. This can be a requirement for enrollment in the study, or can be optional depending upon the design of the study. Patient trial numbers should be substituted for patient names to maintain anonymity for all confidential data sources, especially financial data, as soon as possible. Where economic data are shared with study personnel outside the institution, measures should be taken to remove patient identifying information prior to sharing, if possible. At all times, strict confidentiality procedures should be applied to economic data.

*Economic Evaluation*

In evaluating the costs of cancer in NCI-clinical trials, clinical economics needs to be integrated throughout the development process for cancer therapies, with goals that parallel those of each clinical development stage. The development process allows for timely collection of the data that can be used to evaluate costs and effects of treatments early in their clinical development, with an opportunity for further data collection and evaluation once the therapy has been more widely adopted.

Table 5 depicts the four distinct stages of cancer therapy development. During the first two phases of therapy development, studies are conducted to develop pilot economic data, such as estimates of the mean and variance for costs, quality of life, and utilities for patients with a specific clinical syndrome. These studies are also used to perform pilot tests of data-collection tools, including economic case-report-forms (CRF's) that prospectively capture resources used by patients who will be entered into the phase III clinical trials. From this type of data, sample size for clinical economic evaluations can be calculated. Phase III studies can include economic assessments of new therapies as a primary or secondary endpoint (i.e., economic endpoints can include an assessment of changes in the use of specific resource categories resulting from treatment, such as changes in the use of blood products, changes in the length of hospital stay, or changes in hospitalization rates that result from side effects of outpatient cancer treatment as well as the cost effectiveness of a new therapy). Finally, in Phase IV studies, economic data may be

used to evaluate costs, effectiveness, and adverse events related to the therapy. Again, the economic evaluation can serve as a primary or secondary endpoint of the study.

**Table 5.** Stages of Cancer Therapy Development. [22]

| *Stage* | *Description* |
|---|---|
| Phase I | Therapy is introduced to humans primarily for the evaluation of safety and dosage |
| Phase II | Therapy is introduced into a patient population with the disease of interest primarily for the evaluation of safety and dosage |
| Phase III | Randomized trials comparing safety and efficacy with placebo and/or other therapies |
| Phase IV | Post-marketing surveillance studies |

*Economic Evaluation of Interleukin-3*

The techniques employed to conduct an economic evaluation of a new cancer therapy along side a clinical trial are exemplified in the economic evaluation of Interluekin-3 (rhIL-3) as supportive therapy in patients undergoing autologous bone marrow transplantation.[23] By pharmacologic mechanism, rhIL-3 is a growth factor that regulates the proliferation and differentiation of hematopoietic and lymphoid cells; it is characterized by its ability to stimulate the growth of early progenitors of several lineages, in vitro.[24,25] Both granulocytopenia and severe thrombocytopenia can persist for several weeks following a bone marrow transplant. Granulocyte-Macrophage-Colony Stimulating Factor (rhGM-CSF) and Granulocyte-Colony Stimulating Factor (G-CSF) have both been used to decrease the granulocytopenia that is associated with bone marrow transplantation with much success. However, the persistence of severe thrombocytopenia has continued to remain a great concern. Therefore, rhIL-3 was proposed as therapy to initiate platelet recovery.[26] In a phase III clinical trial, rhIL-3 was assessed in a randomized, double blind, placebo-controlled study of rhGM-CSF and rhIL-3

versus rhGM-CSF and placebo. The clinical trial enrolled patients from 16 different centers.

The economic arm of the study evaluated patients who were enrolled in the trial. Data were collected for both the transplant hospitalization as well as for a period of up to 13 months after the transplant. Data on resource utilization during the hospitalization included length of stay from the clinical case report forms, and hospital bills for each patient. Data associated with specific categories of post-discharge resource consumption were collected via monthly telephone interviews. During each of these interviews, patients were asked about their resource consumption including the amounts of resources used. If patients were rehospitalized during the previous month, the name of the hospital was obtained. Quality of life data was collected using the EuroQol quality of life assessment scale at baseline, three months, six months, nine months, and one year.

For the transplant hospitalization phase of the trial, costs were estimated from patient charges collected from hospital bills. A hospital-wide cost-to-charge ratio obtained from the Medicare cost report data was employed to estimate costs based on patient charges. Missing cost values were imputed using an ordinary least squares regression in those instances where incomplete hospital bills were accompanied by available information regarding resource utilization. Data regarding physician visits were collected, then assigned CPT-4 codes.[18] These codes were then assigned costs using the Medicare fee schedule.[15]

To estimate the costs of care associated with the post-transplant phase of the trial, six cost categories were identified (rehospitalization, chemotherapy, radiation therapy, transfusion, outpatient surgeries and procedures, and provider visits). For rehospitalizations, bills were collected where possible, and costs were estimated, again, by employing a hospital-wide cost-to-charge ratio to hospital bills. Missing cost values were imputed using length-of-stay and an ordinary least squares regression.

Costs for chemotherapy were computed taking into consideration both the cost of the drug as well as physician time. Drug cost was estimated using pharmaceutical wholesale prices while physician time was valued using the Medicare physician fee schedule for chemotherapy administration.[15,18,20]

The costs of radiation therapy were estimated based upon standard regimens using the Medicare fee schedule and included both initial cost components (simulation) as well as costs associated with weekly radiation therapy team visits. [15]

Costs of transfusions (packed red blood cells, white cells, platelet standard unit, platelet apheresed unit, fresh frozen plasma, and whole blood) were estimated based upon proprietary cost data from one University hospital.

Provider costs were separated into three different categories: physicians, nurses, and home health. As discussed previously, the costs associated with physician visits were estimated using the Medicare physician fee schedule.[15,18] Those costs associated with both nurse and home care visits were estimated by multiplying the length of the visit by the hourly cost for each nurse or service, respectively. [27,28]

Outpatient surgeries and procedures were estimated by assigning each procedure a CPT-4 code and assigning a relevant cost based upon the Medicare fee schedule. [15,18]

Finally, missing costs were imputed based upon patient specific means when more than one month of data was available. If not available, the mean cost across all patients was assigned.

This design was successfully implemented, and the results have been submitted for publication. [23]

## Summary

Economic evaluation is playing an increasingly important role in the assessment of clinical treatment strategies for cancer patients. Physicians and patients can use the comprehensive data on the cost and effectiveness of cancer therapies emerging from economic studies to help make treatment decisions. The data from economic analyses will afford clinical investigators an increasingly important tool to help determine the optimal treatment strategies for cancer patients and to help inform health policy decision-makers about the importance of specific cancer therapeutic strategies.

In this chapter, we have outlined a set of procedures that can be used to assess the costs of care within NCI clinical trials. We review the economic framework for assessment of clinical trials, then review a proposed strategy for economic assessment. The design was sucessfully implemented, and the results have been recently published.[23]

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# USING STATE AND FEDERAL CLAIMS DATA TO EVALUATE THE PATTERNS AND COSTS OF CANCER CARE

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## Introduction

Not very long ago, the only codified data that resulted from a clinical encounter was a bill. The remainder of the transaction between a doctor and patient was a typed or handwritten note filed away until the next visit. Burrowing into the files to retrieve enough clinical data to permit a sophisticated outcomes analysis cost considerable time and energy relegating most of these efforts to research centers. Furthermore, the only routine reports at the population level were incidence and mortality data.

Recently, a variety of forces have pressured the health care delivery system to produce high quality information about outcomes of interest to the patient, payor, and policy maker. Variations in practice, such as the widely divergent uses of breast conservation and radical prostatectomy, have raised questions about which of many non-clinical factors affect physician decision-making regarding the treatment for these diseases.[1-4]

Analyses performed using the data physicians and hospitals send to insurance companies or to Medicare contractors for billing show that costs and resource utilization can vary by individual physician, among practices and between regions. For instance, the cost to provide radiation therapy is almost 60% higher in Florida compared to other locations in the United States (US).[5] In this example the differences appear related to the physician ownership of radiation therapy equipment in Florida compared to the rest of the country where hospital ownership

is the predominant model. Other research using claims data show that social and demographic factors play a role in the access to care and were inversely associated with the choice of proper treatment and patient outcomes. For instance, late stage at diagnosis for breast cancer, and the failure to utilize radiation therapy, was associated with living in an urban location, and a low rate of breast cancer cases at the hospital.[6] Many other patient demographic and social factors have been examined such as age, comorbidity, race, education, and type of insurance.[1,7-9]

Most of the examples mentioned above were derived from a careful study of Medicare data, obtained from the Health Care Finance Administration (HCFA), or publicly available hospital data sets. These data were originally collected to bill the government for health care services to the elderly. However, as interest grows in measuring the effectiveness of day-today clinical practice, these data come under more careful scrutiny because they are inexpensive to acquire relative to the cost of a primary data collection, and cover the whole population defined by age and insurance plan enrollment. Further, as Medicare and Medicaid payments climb to a very significant proportion of the total federal expenditure in the year 2000, one quickly appreciates that a careful examination of these data may find opportunities to reduce expenditures. [10]

Secondary data, defined here as the data collected from sources such as insurance claims, discharge face sheets, death certificates, but not directly from the patient or medical record, has assumed an increasingly important role in the quantification of costs and quality of medical care. Secondary data includes not only HCFA claims, but Medicaid data, surveys from the American Hospital Association (AHA), efforts like the Hospital Cost and Utilization Project (HCUP), claims from commercial insurance companies, as well as health-related data files produced at the county, state or national level. Secondary data are usually collected and codified under rules defined by a data dictionary like the International Classification of Disease-9 Clinical Modification (ICD-9 CM) or the Current Procedure Terminology (CPT-4). [11,12]

The purpose of this chapter is to illustrate the advantages and risks of using secondary data for research or policy development employing examples from the published literature. This chapter should help the reader understand: 1) what questions can be addressed with secondary data; 2) a sample of the kind of data available for research; 3) the strengths and weaknesses of these data; 4) the infrastructure required to use these data effectively.

## What questions can be addressed with secondary data?

The gold standard methodology for most clinical research questions is the randomized trial. Randomized trials eliminate selection bias and permit a targeted collection of very specific data. However, secondary data analysis can answer some very specific questions about health care delivery. Claims analysis is particularly useful for examining questions where a clinical trial would be impractical or

unethical. For instance, assessing outcomes in a population by provider report card scores could not be studied by a clinical trial. It would be unethical to randomize a patient to a group of doctors known to deliver poor quality care. Next, the availability of payment data make it possible to determine the cost of a particular episode of care, even when patients receive care at a variety of different billing locations. Because of the large numbers of beneficiaries, these data can be used to estimate trends about treatment patterns for the general population as well as subgroups defined by a factor like age, race, or geographic area. [1] Finally, while clinical trials are performed to determine what treatments affect outcomes, less than 10% of cancer patients in the US are clinical trial subjects. [13] Claims data, on the other hand, reflect the care provided at the community level. Therefore, in some cases it may be possible to use claims to measure treatment outcomes in a more realistic setting than a research facility.

Table 1 shows six examples where secondary data have been used to address a clinical question. For example, data from the Virginia Cancer Registry and Medicare claims were used to study the patterns of care for prostate cancer. [9] The demographic detail from the claims data permitted multivariate statistical analyses which showed that lower age, low comorbidity, rural residence, and later year of diagnosis all were correlated with the increased use of radical prostatectomy. This example also has some limitations. For instance, the lack of specificity about education and income data at the patient level may limit some conclusions about the effect of these factors on treatment choice. Furthermore, the details of staging that most urologists would require to make clinical decisions were incomplete for most patients in the file.

Table 1 also shows how costs can be studied with these data. New cases identified by the Surveillance, Epidemiology and End Results (SEER) system in Western Washington were matched to billing data from the Group Health Cooperative Health Maintenance Organization (HMO) database. [14] These data showed the total costs to the HMO for the major cancers increased with stage for two of the three major cancers and that terminal care costs were similar between cancers. The precise reasons for the differences in cost profiles between tumors, and by age, are difficult to elicit from these data. However, newer data files from HCFA will allow more detailed analysis by type of service (e.g. pharmacy, laboratory, radiology, testing, etc.).

## What data are available?

There are many different sources of data that can be used for cancer-related health services research. There is no central repository for all of these data as they have been generated by the federal government (Medicare, Census Data, National Health Interview Survey, National Medical Expenditure Survey), states (Medicaid, other health and hospital data, and vital statistics), insurance company claim files, the National Death Index, data sets available from commercial sources, the American

**Table 1.** Topics where the analysis of a large database is particularly useful.

| *Topic* | *Example* | *Data Sources* | *Comments* | *Other Examples* |
|---|---|---|---|---|
| Patterns of care within a large, heterogeneous population | Prostate Cancer [9] | Medicare files<br><br>Virginia Cancer Registry<br><br>Area Resource File<br><br>1990 Census data | Age was the primary determinant of treatment choice<br><br>Race and rural vs. urban residence were also strongly associated with treatment predictors<br><br>Comorbidity, census tract estimated income, residence and diagnosis year were correlated with choice of treatment | Lung Cancer [8]<br><br>Effect of comorbidity [15]<br><br>Breast Cancer [39]<br><br>End of life [40] |
| Geographic Variation | Breast Conserving Surgery (BCS) [1] | Medicare claims<br><br>American Hospital Association Survey | 12.1% had breast conservation<br><br>Variation ranged from 3.5% to 21.2%<br><br>BCS more common in small hospitals and where on-site radiation therapy is available | Prostate cancer [3]<br><br>Breast cancer [4] |
| Quality of care | Breast cancer [6] | American Cancer Society database<br><br>Illinois Hospital Association<br><br>Illinois Health Care Cost Containment Council | Late stage diagnosis associated with urban location, poor insurance, and fewer breast cancer cases at a particular hospital<br><br>Omission of radiation therapy associated with urban location and fewer breast cancer cases | Breast cancer [41] |

| | | | | |
|---|---|---|---|---|
| Outcomes in a population | Mortality and reoperation following prostatectomy [42] | Medicare claims<br><br>Manitoba Health Services Commission claims | Excess mortality associated with smaller hospitals, less experience, no teaching program, and open procedure | Hospice [43] |
| Costs | Affect of stage, age, and comorbidity on direct costs for colon, prostate and breast cancer [14] | Group Health HMO database<br><br>SEER Registry | Total costs increased with stage for tow of three cancers<br><br>Terminal care costs were similar among cancers | End of life costs [44]<br><br>Last year of life [45]<br><br>Colorectal follow-up [46]<br><br>Medicare use by cause of death [47] |
| Effect of specific reimbursement system | Effect of HMO vs. FFS reimbursement on care of colon cancer [18] | Medicare claims | HMO patients had more screening tests<br><br>FFS patients had more imaging<br><br>No significant difference in quality or patterns of care | Presenting cancer stage [48] |
| Epidemiologic studies | Cancer incidence using claims files [22] | SEER<br><br>Medicare | Incidence rates of 4 of 6 cancers differed between the two sources by <5%<br><br>Higher variation for prostate and esophogeal cancer | Lung cancer [21] |

Hospital Association, and area resource files compiled by state or research organizations. Table 2 lists some of the data that are available for cancer-related research. The list is not exhaustive but highlights sources that have already been used in the peer reviewed literature.

These data become even more useful if they are linked to sources that contain complementary information. For instance, data from the Virginia Cancer Registry were linked to Medicare files to determine statewide patterns and costs of cancer care as well as the influence of comorbidity on breast cancer treatment. [8,9,15] Complex algorithms and matching software have been developed to accomplish this task. [16] These linkages permit more sophisticated analyses, with a high degree of statistical accuracy, using the patient as the unit of analysis. Other analyses can be performed using the hospital, state, or type of health care system as the analytic unit. [3,17,18]

## Analytic Framework

Once the researcher obtains permission and guarantees confidentiality of data, access to secondary data is relatively straightforward. Once the data are obtained, cleaning the data to obtain a final data set for analysis requires significant time and expertise. These files can range in size from thousands of megabytes to gigabytes in size often requiring significant computing power to simply run the data for cleaning. The researcher must understand the variables in each of the data sets and obtain a data dictionary from the source. It is essential to maintain contact with the experts from whom these secondary files are obtained because information on the utility of the variables is not reported in the data dictionary. Working with millions of records requires a different approach and set of skills than more traditional analyses using smaller data sets. It is essential to evaluate the data carefully by performing many descriptive analyses because it is impossible to assess data quality by a direct examination of this volume of raw data.

Getting useful information from the data requires a well planned analytic framework. Mitchell [19] et al provide a useful guide to building episodes of care with large data sets which involves three steps: 1) case definition; 2) define the episode; 3) measure outcomes.

The following example is proposed to show this process in a real situation. Investigators at the Medical College of Virginia received a grant from the Agency for Health Care Policy and Research (RO1HS 0689-01A1) to determine the patterns and costs of lung cancer care in Virginia. [20] Data sources included the Virginia Cancer Registry and the Medicare Annual Demographic Files, the Medicare Provider Analysis and Review files (MEDPAR), the Medicare Health Insurance Master File (HIM), the Medicare Automated Data Retrieval System (MADRS) file, the Area Resource File (ARF) and the 1990 Census Data for Zip Code Level Information(Tape3b).

**Table 2.** A sample of sources of secondary data available for cancer research.

| *Source* | *File* | *Major Contents* |
|---|---|---|
| Medicare Files<br>www.hcfa.gov* | MEDPAR (Part A) | Acute care hospitalization, skilled nursing facilities. Has up to 9 ICD-9 CM diagnostic codes and 5 ICD-9 CM procedure codes |
| | BMAD-IV (Part B) | Physician bills, outpatient claims, home health, x rays, laboratory tests, and durable medical equipment. Available for 100% of all services and include a primary and 3 other ICD-9 CM diagnostic and a CPT code |
| | | Contains limited data on every person enrolled in Medicare for each year |
| | Denominator File | Socioeconomic data, health status, satisfaction, access to care, claims, payments and a detailed survey on a limited sample of beneficiaries |
| | Current Medicare Beneficiary file | Inpatient, outpatient and other health resource utilization and costs (available since 1991). |
| | National Claims History | |

| | | |
|---|---|---|
| Commercial insurance claims data [44] | | Similar to Medicare but occasionally contains pharmacy and expanded outpatient data. Quality varies widely. |
| SEER-HCFA linked files [29] | | All Medicare data plus clinical characteristics (stage, comorbidity, tumor size, etc) from the SEER registry population who are also enrolled in Medicare. |
| Medicaid Statistical Information System<br>www.hcfa.gov | Multiple files | Voluntary submission of data form over 28 states on eligibility, utilization, payments. Local data may include pharmacy, laboratory and x-ray data while Medicare does not. |
| Area Resource File [8]<br>www.ssdc.ucsd.edu/ssdc/90 | | Health care resources by area (e.g. hospital beds, radiation facilities, number of physicians, etc.). |
| American Hospital Association<br>www.amphi.com | | Information on bed utilization, hospital resources |
| Census Data [9]<br>www.census.gov | | Permits linkage with location code (such as zip code or county) to provide total, age, race and sex specific population estimates as well as estimates of income and education. Multiple files with multiple files of detail. |

## Case Definition

Constructing the episode of care in this example is relatively simple because the VCR contains the diagnosis date, the tumor subtype, and stage. By definition, this population was all over 65 years old. Cases used in the analysis were all lung cancer patients (ICD-9-CM 162) with the exclusion of patients who were diagnosed at autopsy, or had in situ cancer, a previous cancer documented in the VCR, or had their diagnosis and treatment dates in the VCR and Medicare files differed by more than two months. Of 7,817 lung cancer cases in the linked file, 4,999 were used in the final analysis.

When insurance claims cannot be linked to an incidence-based registry, or if a question related to a complication is the focus of study, the issue of case definition becomes more complicated. In this situation, distinguishing incident from prevalent cases is difficult. Algorithms have to be created that link an ICD-9CM diagnostic code with a one of several ICD9CM procedure codes to define an incident case. However, this approach may have a lower sensitivity for case detection. [19] Searching many years of previous data has been used to eliminate prevalent cases, but this approach requires more computer resources and experience managing files. [21,22]

*Defining the Episode*

Close scrutiny of the data for the lung cancer example showed that some treatments were provided before the VCR documented the diagnosis (i.e. an outpatient biopsy was not discovered by the tumor registry and radiation therapy was prescribed as an outpatient so the patient was not registered in the VCR until later in the illness). Therefore, the patterns of initial treatment required us to define the episode as any cancer treatment procedures that occurred between 45 days prior and 6 months following the VCR diagnosis. Five mutually exclusive categories of initial therapy were defined: no treatment, surgery, radiation therapy, chemotherapy and combinations of therapies; data were searched by and ICD-9 CM codes for the various treatments.

There are several pitfalls in defining the episode using claims data which include: 1) the inability to determine how long an episode commonly lasts (e.g. is radiation therapy beginning three months after surgery a combined treatment or a new therapy for recurrent disease? Tumor registry data do not answer this question); 2) neglecting the costs and tests generated by the illness before the episode begins; 3) deciding which events and procedures are attributable to the episode and which are part of an unrelated illness (e.g. is a pneumonia diagnosed six weeks after chemo-radiotherapy a complication of treatment or an unrelated problem?)

*Measuring Outcomes*

This is the greatest challenge to the use of claims data. Medicare (and most commercial insurers) lack the clinical detail to determine the success or failure of a particular treatment. [19] Mortality is an easier outcome to track for Medicare using the data from eligibility records, but may be impossible for commercial claims data because date of death is not coded and patients may switch policies at any time.

For the lung cancer example the mortality issue is fairly clear. Moreover, the median life expectancy for lung cancer patients is less than a year so several years of claims data are usually sufficient to track the mortality rate of a lung cancer cohort. Furthermore, most tumor registries attempt to capture the relapse and death dates of cases but vary in their success. Tracking outcomes other than death are very difficult and were not attempted for this lung cancer population. Using the diagnostic and procedural code detail embedded in Part A and Part B claims may occasionally be useful to track complications but the lack of clinical detail make it impossible to attribute the cancer, treatment, or underlying comorbidity as the cause of intercurrent events. For cancers with a longer natural history, claims can be used to determine recurrences by creating algorithms that define expected treatments that occur a certain time after the primary cancer is treated. However, these data are not sensitive to cases where the cancer recurs but fails to create a billing event that triggers a new disease status, or when a patient changes insurance. The latter problem is uncommon for Medicare since all are enrolled until death.

*Adding Detail*

One of the central themes of the lung cancer analysis was to determine if patterns of treatment varied by clinical, demographic and socioeconomic factors. To broaden the detail for each patient, their zip code of residence (from the Medicare file) was linked to the Area Resource File for Virginia and Census Data (from the Census Bureau). These linkages permitted the investigators to examine the use of various lung cancer treatments by social class (education and income at the census block and tract level), urban vs. rural residence, and availability of surgical and radiation therapy specialists and equipment.

*Measuring Costs*

Medicare and commercial insurers keep detailed data on their reimbursement for the professional and technical aspects of their beneficiaries. Medicare files usually contain both Part A and Part B payments. However, Medicare payments may under represent total cancer payments because some elders use commercial insurance (Medigap) to cover copayments, physician bills, and pharmaceutical costs. Indirect costs (out of pocket costs, family costs etc.) are never included in these files. Technically, Medicare reports payments, not costs or charges. Neither payments nor charges reflect costs although Medicare payments are much closer to costs than the negotiated rates paid by commercial insurers.

Total and treatment-specific lung cancer costs were measured for those patients according to their survival status at one year. Comorbidity adjustments were made using the Dartmouth-Manitoba conversion algorithm for modification of the Charlson comorbidity index.[23,24] Episodes of care for the cost analysis spanned one year from diagnosis. No attempt was made to "subtract" the costs of comorbid illnesses in this group.[l4,25] In this example Medicare payments for lung cancer patients in Virginia were compared to lung cancer payments made in areas with the SEER system and were shown to be substantially lower.[26,27]

## Strengths and Weaknesses of Claims Data for Cancer Research

Claims data analysis can be an efficient and powerful tool to examine the effect of diagnostic tests, treatments, or social factors on outcomes for a population of cancer patients. Table 3 summarizes the strengths of these data. Administrative data are already computerized and codified; there are standard approaches to diagnostic coding which allow it to be compared from one geographic site, health plan or hospital to another. The presence of other diagnostic codes in the data permits adjusting the comorbidity level so that two populations can be compared. [24,28] Further, these data are relatively inexpensive, accurate (at least for inpatient cancer diagnoses), and are longitudinal.[29] The longitudinal aspect of claims data make these data more useful than tumor registry information especially later in the course of the illness or for outpatient diagnosis and treatment.

There are substantial weaknesses however. It is important to always remember the ultimate purpose of claims data is a request and justification for payment. Therefore, the clinical data are sparse and the coding order or context may be altered to maximize reimbursement. [30] While comorbidity assessment is important, this can be problematic for patients with several chronic illnesses (especially cancer) because until recently there were only five diagnostic code lines on the Medicare Uniform Billing form. [31] Some diagnoses (i.e. peripheral vascular disease and congestive heart failure) are often not coded accurately which reduces the ability to adjust for severity of illness. [29]

The accuracy of claims data have been compared to tumor registry and medical record information. Table 4 shows data about the accuracy of claims data compared to various tumor registries. When SEER rates and Medicare rates for the same population (but not linked to individuals) are compared, the incidence rate of each source is within 6% of the other. [32] In Virginia, the incidence rate using linked, person-level data for various cancers were also similar between the VCR and the Medicare files. However, there was a substantial mismatch between data sources so that only 70% of the prostate cancer cases identified by Medicare were found in the VCR and only 81% of colorectal cancers identified by the VCR were found in the Medicare files. [33] These investigators found that the two sources identified a different, but overlapping, group of patients. When the two data sources were used together the aggregate sensitivity ranged from 92% to 97%

depending on tumor type. Several reports show that diagnostic coding can be inaccurate. [34,35] However, the discrete nature of the cancer diagnosis, defined by a pathologic determination rather than a clinical impression, reduces errors based on the judgment of the coder. [36]

**Table 3.** Strengths and weaknesses of using administrative data for cancer research.

| *Strengths* | *Weaknesses* |
|---|---|
| Computerized and codified for simpler analysis | Payment focused, so clinical data superficial |
| Stable longitudinal data | Coding errors common and may be biased to maximize reimbursement [30] |
| Answers questions that a randomized clinical trial cannot address | Comorbidity assessment imperfect because of limited lines on Medicare form [31] |
| Representative of the population because of large sample size | Not specific for disease severity for some common diseases [29] |
| Data collected uniformly with codified definitions of disease states | Unable to report stage or clinical detail |
| Screening for outcomes [35] | |
| Comorbiity estimates possible [24, 28] | |
| Relatively inexpensive | |
| Lacks reporting bias common in clinical trials | |
| Highly accurate for inpatient-based cancer diagnosis [29] | |
| More current than most registries | |
| Captures outpatient data which is typically not available to hospital registrars [29] | |

**Table 4.** Comparing the use of claims and tumor registry data to estimate cancer incidence.

| *Data Source* | |
|---|---|
| *VCR and MEDPAR Comparison* [33] | *Sensitivity for detecting incident cases* |
| VCR compared with population estimate | .70 - .82 |
| MEDPAR compared with population estimate | .73 - .83 |
| Both sources aggregated and compared with population estimate | .92 - .97 |
| *Seer and Medicare comparison* [32] | *Incidence of cancer (per 100,000)* |
| Medicare claims | 285 |
| SEER | 302 |

## Infrastructure

The low cost, large sample size, availability of payment information and richness of secondary data have stimulated a great deal of research and commercial interest in these methods. Health services researchers realize the potential of tracking the costs and patterns of care over time. Insurers and disease management companies can case rates on this information. Epidemiologists can measure cancer incidence in areas where registries do not currently exist. However, the use of these data require special systems and analytic skills.

Medicare claims files are large. In 1991 alone, inpatient and skilled nursing stays generated almost 13 million discharge summary records; outpatient visits more than 60 million bills; and physicians and related providers more than 500 million bills. [19] It is not surprising that the use of these data can be frustrating without attention to the infrastructure required to produce high-quality information in a reasonable period of time. Table 5 shows some of the issues that need to be considered to examine data of this magnitude. Requirements to manage large sets of data include:

- a programmer/analyst who has experience managing large datasets. There are many details about how claims are stored, updated, and changed over time that need careful documentation and management

- epidemiologic and statistical expertise
- adequate computer storage, processing speed, and analytic software
- strict confidentiality procedures so that patients, providers and specific institutions cannot be identified [37, 38]
- clinical input

**Table 5.** Infrastructure required to perform claims analysis for cancer research.

| *Element* | *Comment* |
|---|---|
| Database Programmer | Programmer/analyst needs to be experienced in the analysis of large claims file |
| Epidemiologic and statistical expertise | Necessary to coordinate statistical analyses, judge adequacy of samples |
| Clinical support | Clinical input is very important to test alternate explanations for findings as well as determine validity in certain clinical circumstances |
| Computer expertise and adequate hardware | Some claims files are at least 3-4 Gb, requiring sufficient storage and processor speed to analyze large data sets |
| Relationship with the data supplier | Most data sets have idiosyncrasies and errors that can only be explained by the programmer who devised the data set or who has used it before |

## Conclusions

Secondary data are a valuable source of information for many kinds of cancer research. The longitudinal collection of data on processes of care, outcomes and costs have led to important findings about how cancer is treated as well as the economic burden of this illness. The ability to link these data to tumor registries or other clinical information sources enhances the validity and clinical usefulness of the analysis. Furthermore, the ability to aggregate payments over time by specific

clinical factors may permit insurers or providers to understand their cost variation and to search for more efficient patterns of care.

The limitations of these data in drawing conclusions about why costs are high or certain patterns of care are observed cannot be overemphasized. However, a carefully planned analysis may offer powerful insight into quality and practice variation that require greater attention. Rarely do these data supplant the need for clinical trials about the efficacy of procedures, drugs and tests.

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# COSTS OF CANCER CARE: IS THE COMMUNITY SETTING DIFFERENT THAN THE ACADEMIC?

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## Introduction

In 1992, shortly after the election of President William Jefferson Clinton, a government led initiative for health care reform was begun. Driving factors included considerations related to both costs and access - unabated increases in health care costs, accounting for 12% of the Gross National Product, 30 million Americans without health care, employers' health care contributions continuously rising, and health care insurance plans that were not portable and were difficult or very expensive for individuals with pre-existing illnesses. The Federal health care reform initiative began in 1993 with a series of closed meetings, with a plan presented to Congress in 1994. The Clinton plan called for "managed competition" by health care insurers, health maintenance organizations (HMO's), and the creation of hospital-physician networks that would compete with one another in the marketplace. A decrease in health care costs would be possible through efficiencies in medical care, decreased administrative costs, reduced variations in care, and improved outcomes. New buzzwords including clinical protocols, continuous quality improvement, total quality management, and managed care were being incorporated into the health care reform lexicon. Despite the tremendous amount of time and effort devoted to the reform package, the Federal initiative failed.

Nonetheless, in 1997, health care reform is occurring, with business leaders taking the central position. The practice of oncology is changing dramatically, as small physician groups coalesce into larger groups, and large groups join national cancer programs such as American Oncology Resources, Physicians' Referral Network, and the Salick HealthCare Network. Oncologists are being challenged to provide high quality care that can be viewed as good "value".

## Obtaining Value in Oncology Care

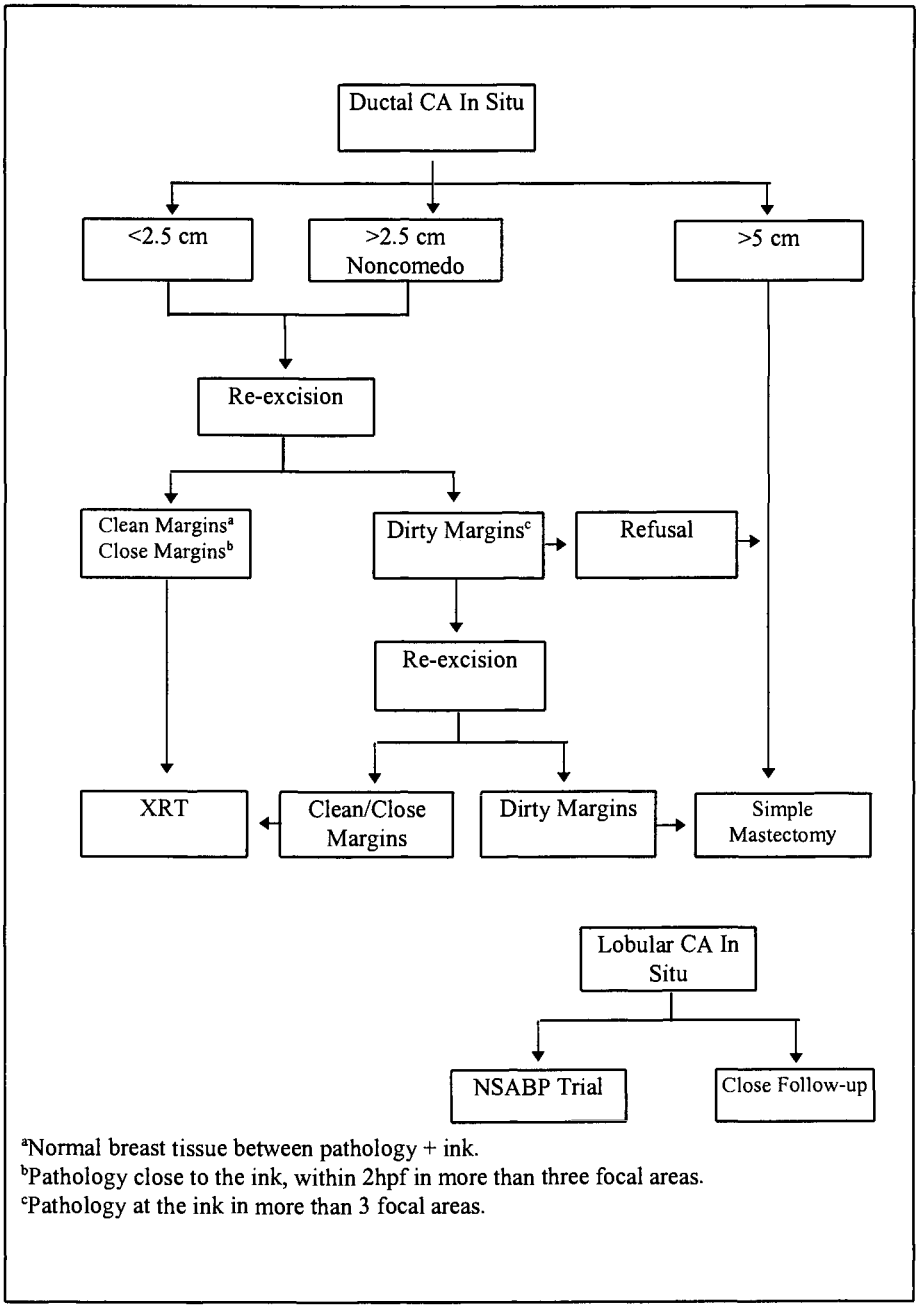
Health policy analysts stress the need to maximize health care value, given the current necessities to consider costs in all aspects of medicine. Value is defined as the ratio of quality of health care to costs of care and is often operationally measured as dollars per year of life saved or, more recently, as dollars per quality adjusted years of life saved ($/QALYS). As an example, at our community oncology setting in Chicago, we have evaluated alternative treatment strategies for early stage Hodgkin's disease, looking for the treatment option that provides the best overall health care value for our patients. We estimated that medical charges for 100 patients with stage I or IIA/B Hodgkin's disease who are staged in identical manner (without a staging laparotomy) and treated with doxorubicin, bleomycin, vincristine, and dacarbazine (ABVD) chemotherapy for a median of 8 cycles and followed for 5 years would be $1.93 million. For the expected 87 patients who achieve a curative result, estimated annualized charges would be $4,430 per year of life saved. In contrast, if the same 100 patients had been treated with radiotherapy (for the expected 65 patients who have stages IA/IIA) or radiotherapy and chemotherapy (for the expected 35 patients who have stages IB/IIB) and followed for 5 years, the estimated total charges would be $2.04 million, reflecting additional radiation therapy changes. For the 90 patients who achieve a curative result, the annualized charges are estimated at $4,522 per additional year of life saved. In both scenarios, while the actual costs would be significantly lower, the relative differences between the two treatment options would not change dramatically. Therefore, in our community oncology setting, we have chosen to treat early stage Hodgkin's disease with ABVD chemotherapy, because it is clinically effective and, in comparison with the alternative treatment option, it provides better value.

This model speaks to the issues that practitioners must address, regardless of their affiliation with community or academic practice settings. Considerations of costs, effectiveness, and cost-effectiveness are required in designing optimal treatment strategies. The changing organizational structures in oncology is an important cofactor in these considerations. Large oncology practices are able to aggregate clinical and economic data on groups of patients and identify practice-specific estimates of total costs for alternative treatment strategies. In other treatment settings, different strategies may be chosen as providing the best value because of variations in local costs, rather than differences in technical abilities of the medical or radiation oncologists.

## Guidelines

With the economic pressures resulting from steadily decreasing reimbursement rates, all oncology practices are looking for ways to control costs. Many oncologists have directly adopted published guidelines or developed their own. At the Lutheran General Hospital Cancer Care Center we have derived locally developed consensus algorithms for both diagnostic and therapeutic care. Our philosophy in each guideline effort is to encourage patient participation. However, since many patients do not desire active participation in all phases of cancer care, we have also developed treatment protocols in order to decrease practice variation and lower overall health care costs, while providing high quality patient care. These protocols are based on local consensus of all the providers in our practice. Subsequently, we have begun to monitor the practice patterns of individual providers, identifying outliers in practice style, and incorporate feedback and other continuous quality improvement initiatives into our practice. For each of the treatment protocols that we have derived, we have estimated the potential value of the therapy, based on our current charge structure and our expected clinical outcomes. For example, based on the algorithms shown in figures 1-4, our estimated costs of providing care for women with breast cancer range from $510 to $31,200 per additional year of disease free survival. Therefore, we view the breast cancer guidelines as one example of a local guideline effort that allows us to provide cost-effective care.

Supportive care strategies are also included in our guideline efforts. At Lutheran General Hospital, the second most common cause of hospital admissions is neutropenic fever following chemotherapy. In 1984, 654 patients were admitted for neutropenic fevers, accounting for 3,401 hospital days and almost $5,000,000 in hospital charges. The American Society of Clinical Oncology's guidelines on hematopoietic colony stimulating factor use have also been incorporated into our practice following their publication in 1995. Compliance has been greater than 75% among the Division members. In January 1996, the Division identified neutropenic fevers accompanying chemotherapy as a primary target for guideline efforts. A locally developed outpatient antibiotic regimen for neutropenic fever (led by Steven Devine, M.D., Director of Bone Marrow Transplantation) was adopted. All chemotherapy patients who developed neutropenic fever and did not have a sepsis syndrome were examined in the ambulatory setting and started on Ciprofloxacin 500 mg p.o. q12h, fluconazole 400 mg p.o. q24h, and rifampin 400 mg p.o. q12h. Patients were seen daily and antibiotics were changed based on the algorithm. Criteria for admission included positive blood cultures, unstable vital signs, non-compliant patient, or persistence of fever. As of October 31, 1996, the number of admissions for chemotherapy related neutropenic fevers is




[a]Normal breast tissue between pathology + ink.
[b]Pathology close to the ink, within 2hpf in more than three focal areas.
[c]Pathology at the ink in more than 3 focal areas.

**Figure 1.** Guidelines for Breast Cancer In Situ.

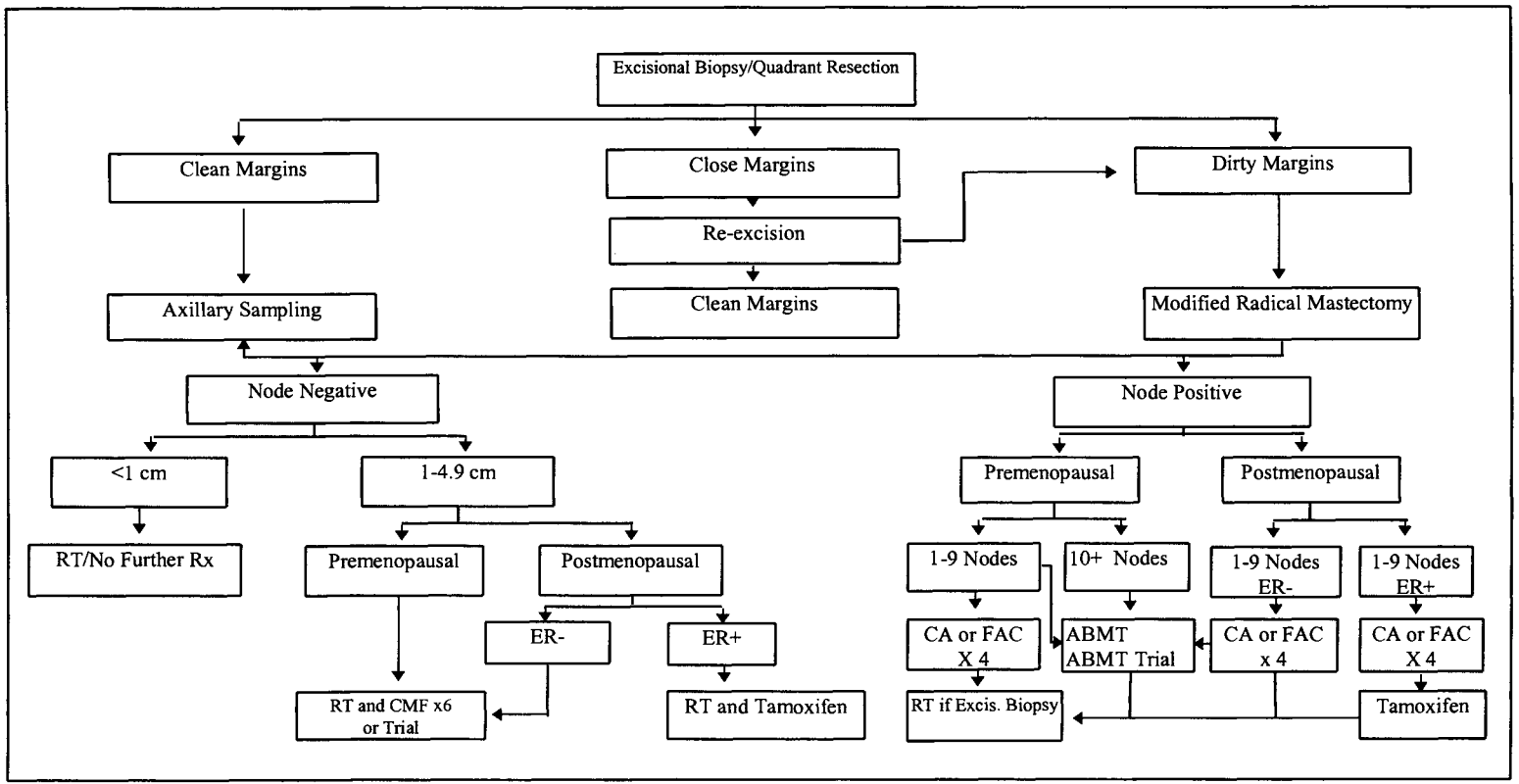



**Figure 2.** Invasive Breast Cancer <5 cm (Clinical Stage I and II)

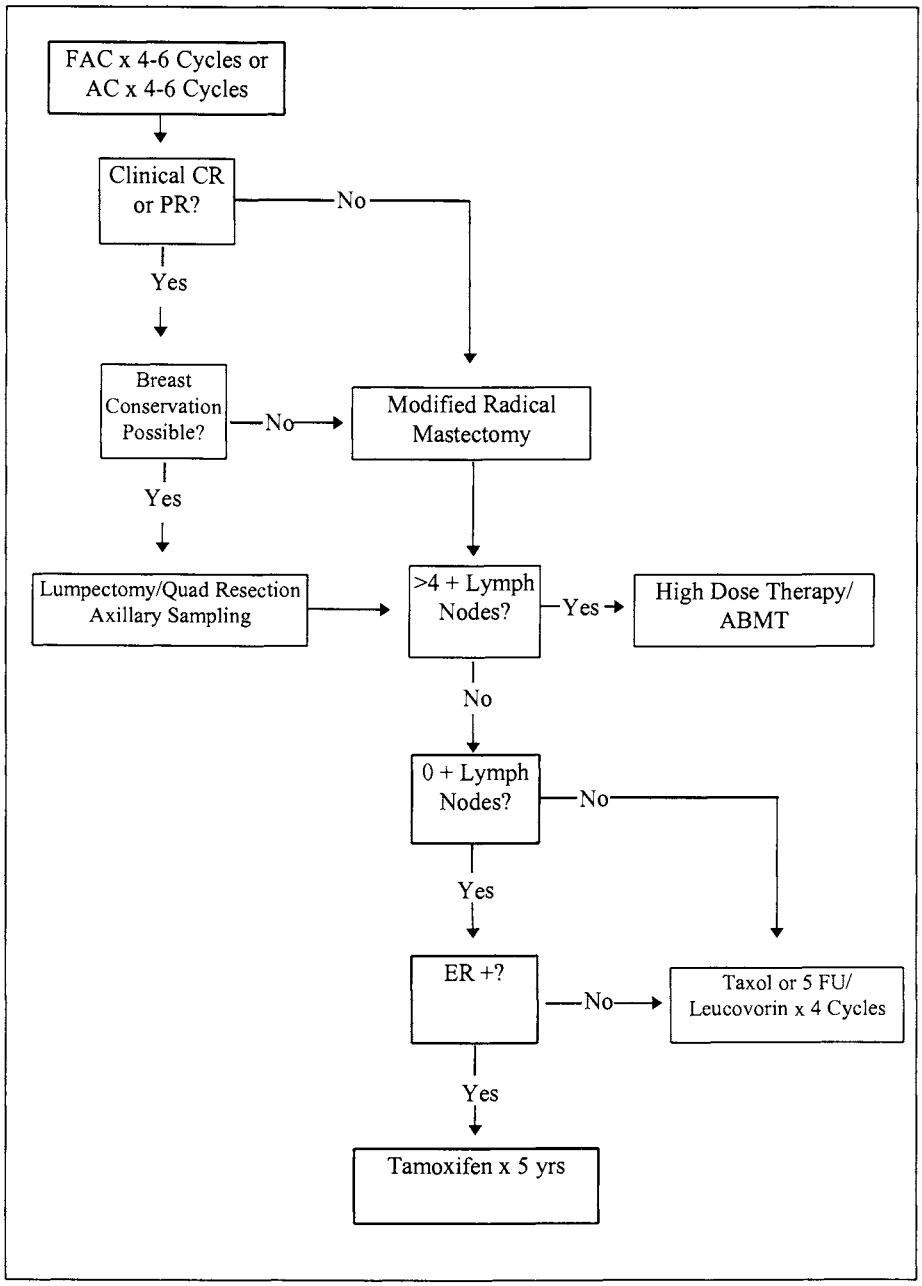



**Figure 3.** Breast Cancer Stage IIIA and IIIB.

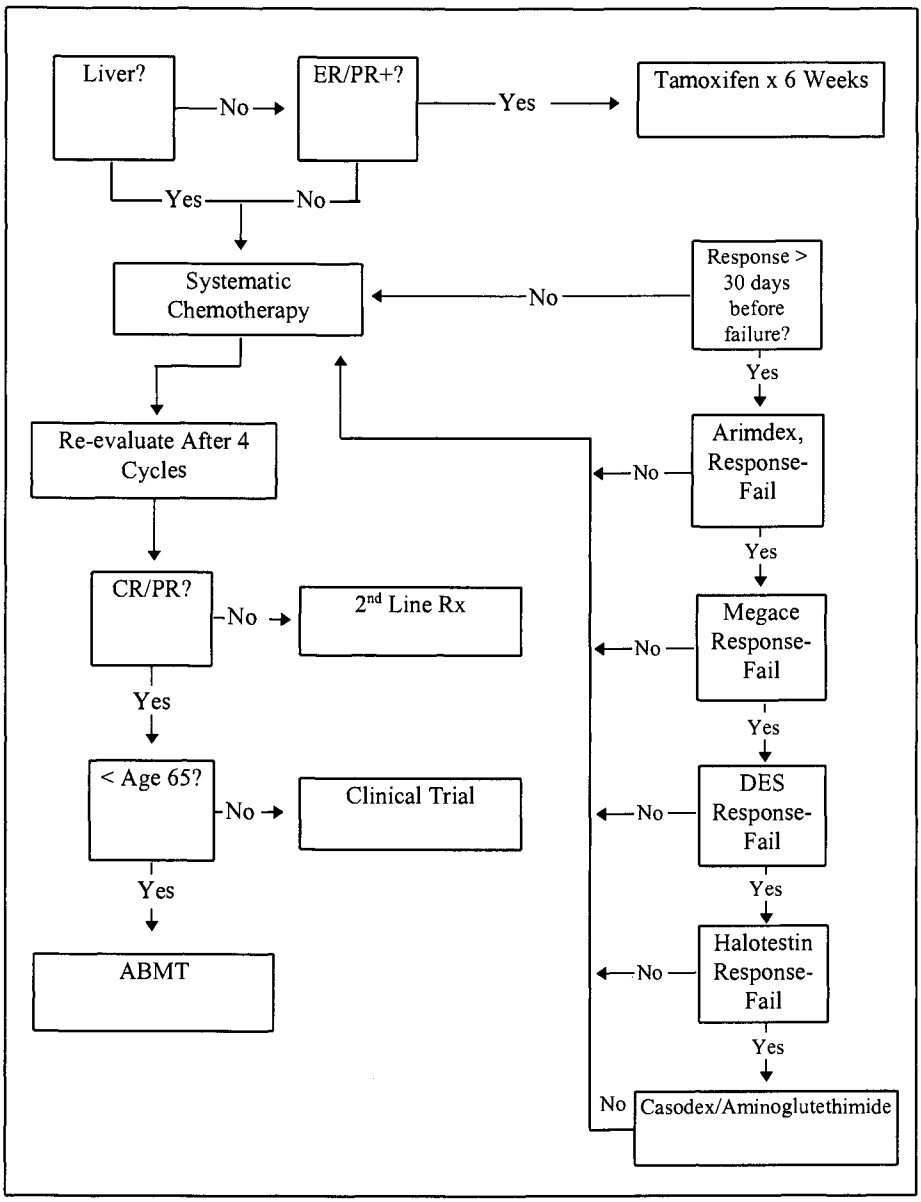



**Figure 4.** Breast Cancer Stage IV.

221, accounting for 1105 inpatient days. On an annualized basis, we expect to see a 60% reduction in hospital admissions for neutropenic fevers and a 61% reduction in hospital days, with a net savings of $2.2 million. Other locally developed guideline efforts are likely to provide similar value for our practice. For example, by using an algorithm for prophylaxis for patients receiving autologous bone marrow transplantation and delivering chemotherapy and total body irradiation in the ambulatory setting, we have been able to decrease the hospital length of stay from 19 days to 12 days and realize a per case savings of $31,315.

While academic centers choose to form national networks such as the National Comprehensive Cancer Network (NCCN) and develop national guideline strategies, we have chosen a local approach to health care. Our guidelines take into consideration local practice styles, availability of resources in our health care system, and general characteristics of our patient population, and are specifically designed for our market area. Because of local buy-in at all steps in the guideline process development, we have had little problem implementing the guideline effort and continue to develop efficient continuous quality improvement efforts to evaluate their implementation.

## Organizational Changes

As a consequence of the shift in cancer care from the inpatient to outpatient setting, inpatients are generally sicker than in previous years and consequently, the intensity of services required for individual inpatients has increased. In an effort to provide the required services in a cost-effective manner, we have examined how resources and personnel are used in the delivery of inpatient care, with an initial focus on supportive care. In our hospital, anti-emetic care was one of the first areas that we targeted. Based on pharmacy, nursing, and physician input, we determined that oral ganisetron is as effective, less expensive, and required less pharmaceutical preparation time than its intravenous counterpart. We subsequently developed and implemented a guideline that allowed for use of oral and intravenous anti-emetic therapy, based on severity of emesis and other clinical factors. Second, we addressed the area of inpatients with neutropenic fevers, and developed a treatment protocol to parallel our previously developed outpatient protocol. The original algorithm, developed in early 1996, is already being updated. Vancomycin is an expensive antibiotic which was included in the original protocol. However, with the growing emergence of vancomycin resistant enterococcus (VRE), we have removed the drug from the treatment protocol. By using fourth generation cephalosporins, such as Cefepime, which can be administered twice daily rather than three times daily, we anticipate decreasing costs, by lowering labor costs associated with intravenous antibiotic preparation and administration. For patients undergoing autologous bone marrow transplantation, prophylactic oral antibiotics with oral ciprofloxacin and rifampin are used, resulting in fewer hospitalizations and lower costs.

A second area of change is related to increased dose -intensity of women with breast cancer. We have initiated a program for tandem autologous bone marrow transplants for stage IV breast cancer. The initial transplant was performed entirely in-hospital at an average charge of $76,900, while the second transplant was performed entirely as an outpatient at an average charge of $16,440. We have also incorporated outpatient total body irradiation into the transplant program. The total transplant charges, $93,300, represent a 50% reduction from a single transplant performed 5 years ago in our hospital.

## Conclusions

Examining the costs of care without evaluating the effectiveness of alternative therapies is not sufficient in today's competitive health care environment. New organizational, intellectual, and administrative approaches to cancer care are needed in order to respond to the challenges of health care reform. Community oncology providers are in a position to take a leadership role in these changes through programs that incorporate locally developed consensus guidelines, treatment protocols, and continuous quality improvement methods.

# HEALTH SERVICE STUDIES IN THE TERMINALLY ILL CANCER PATIENT

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## Introduction

There is a crisis in both health care spending and health care quality in the United States, regardless of our ability to ignore it. Even with projections of a budget surplus by the year 2003, the plan is still to cut Medicare by $115 billion over the next five years. Cancer care costs have risen from $35 billion in 1990 to $40 billion in 1994 to one projection of $50 billion by 1996.[1-3] Of the $191 billion spent on Medicare patients in 1996, $34 billion was spent on cancer fee for service care (Personal communication, R. Lee, Accountable Oncology Associates, 1997). Nearly one third of all Medicare spending is on patients in their last year of life; although this may be medically appropriate care, those dollars cannot be spent on preventive services or chronic disease conditions for the same population.[4-6]

At the same time, evidence is accumulating that the care given to patients in their last phase of life is sadly lacking in quality. The SUPPORT study showed that half of all dying patients had needless pain and suffering in their final days of life while in the hospital.[7] In the outpatient setting, there is substantial evidence that nearly half of the patients suffer needless pain even when cared for by oncologists or academic oncologists.[8] There is substantial evidence that the care given to cancer patients may be suboptimal, although this has been studied infrequently. For breast cancer, substantial practice variation by geographic region has been documented with some states having five times the number of mastectomies versus the preferred method of breast conserving lumpectomy and radiation.[9,10] Hillner et al

documented substantial under use of adjuvant therapy; and under use of surveillance mammography in patients after breast cancer treatment, with about 20% having no follow up mammogram within two years.[11,12] Smith et al documented substantial under use of aggressive thoracotomy in the elderly with lung cancer compared to younger patients, and Desch et al documented the same pattern in prostate cancer.[13,14] Others have reported similar findings of suboptimal care in breast cancer.[15,16] The effect of this less than optimal care cannot be quantified with current information (partly because it would be difficult to randomize a cohort to suboptimal care), but it is clear that the process of care may not be optimal for all patients.

The effect of increased demands for care from an educated elderly population, more elderly long term survivors, new and expensive technologies, new diseases like acquired immunodeficiency syndrome, and demands for cost cutting makes the allocation of health care dollars a "political nightmare" for those who attempt it.[17,18] And these concerns filter down to the individual bedside, too. Families who were financially strapped were more likely to choose supportive care rather than aggressive care for their loved ones in the ICU, although this may be more appropriate medicine, it is an unintended consequence of our current implicit system of rationing based on ability to pay.[19]

In this chapter, we will review the available studies of health service research and palliative care.

## Methods

We reviewed Medline from 1980 to 1997 for relevant English language articles, and did comprehensive selected searches within bibliographies. We excluded information in abstract form only, and studies that focused only on quality of life.

### *Data Available to Decision Makers*

We have tried to organize data in a way useful to decision makers presenting clinical and cost information side by side if possible. The major categories are shown in Table 1.

### *Chemotherapy versus Best Supportive Care*

This topic has probably consumed too much public and professional debate as these strategies are too often considered mutually exclusive, when both are trying to help the patient. We and others have argued that chemotherapy for incurable solid tumors is generally worth trying for symptom relief or to prolong survival. The key is to make the switch to supportive care while resources and good quality time are still available.[20]

**Table 1.** Types of studies of health and service research studies.

| *Type of study* | *Question posed* |
|---|---|
| Type of care: chemotherapy vs. best or other types of supportive care chemotherapy | Does chemotherapy save money compared to best supportive care, when all costs are considered? |
| The site of service | Is home vs. hospitals more effective and less costly? |
| Structural and process changes in care | Can costs of care be reduced by changes in how it is delivered? e.g. by coordination or at home? |
| Hospice vs. non hospice | Does hospice improve quality of life or reduce costs of care? |
| Advanced directives and Do Not Resuscitate Orders | Do advanced directives influence medical treatment decisions or change costs? |

In the available studies, chemotherapy has generally proved to have a positive impact on clinical outcomes, and to be within acceptable bounds of cost effectiveness (Table 2). Given reporting bias, this conclusion cannot be generalized to any regimen not formally studied. The American Society of Clinical Oncology has outlined appropriate outcomes that justify therapy in cancer patients.[21]

The Expert Panel could not define a minimum amount of benefit required to justify treatment, but a least some benefit in symptoms or disease control was required. Several recent studies may call even these simply demands for benefits into question. Slevin et al found that dying patients would undergo almost any treatment toxicity for a 1% chance of short term survival.[22] A study of palliative radiotherapy for brain tumor patients showed no survival or function benefit, and a substantial decrement in intellectual function, but most patients and families would still desire it.[23,24]

The acceptable bounds of cost-effectiveness ratios deserve an explanation. Laupacis and colleagues in Canada have suggested the following hierarchy: 1) treatments that clearly work and are less expensive be adopted readily; 2) those with cost-effectiveness ratios <$20,000 per additional year of life (LY) gained be accepted with the recognition that they cost additional resources; 3) that treatments with cost effectiveness ratios $20,000-$100,000/LY be examined on a case by case basis with caution; 4) and that treatments with cost effectiveness ratios of >$100,000/LY be rejected.[25] This system has validity in a socialized medicine

system where all resources are shared equally; it is not clear how this system applies to

**Table 2.** Comparison of Follow-up Plans.

| *Test* | *Shoemaker, Standard Group* | *National Cancer Center Network* | *Society of Surgical Oncology* | *NSABP* |
|---|---|---|---|---|
| History and Exam | 3-months x 2y<br>6-months x 3y | Similar | | 6-months x 5y<br>then yearly |
| Fecal occult Blood | Yearly | Yearly | | 6-months x 5y<br>then yearly |
| CBC<br>LFT | Yearly | | | 6-months x 5y |
| CEA | 3-months | | | 6-months x 5y |
| Colonoscopy | Every 5 years | | | At 12 months,<br>3 years follow |
| CXR | As indicated | | | 12 months x 5y |
| CAT | As indicated | | | As indicated |

other health care systems where resources may not be shared.[26] For instance, should patients be allowed to purchase additional insurance for expensive treatments, or pay for them out of pocket? In the United States, there has been no accepted answer but most authorities have agreed on an implicitly defined benchmark of $35,000-$50,000 per year of life saved.[27]

*Lung Cancer*

Chemotherapy for non small cell lung cancer adds some small benefit, estimated at 2-4 months in most series, and gives symptom relief in up to 60% of patients in the studies which have measured this.[28-30] For this reason, both the American Society of Clinical Oncology and Ontario government recommend consideration of chemotherapy for suitable patients.[31,32] In the only available economic analysis, Jaakimainen et al found that chemotherapy actually saved disease management costs compared to best supportive care by preventing hospitalizations late in the disease course. The cost effectiveness ratios ranged from $-8,000 (cost saving) to $+20,000 Canadian for each additional year of life.[33]

Smith and colleagues found that chemotherapy with cisplatin and vinorelbine, compared to vinorelbine alone or cisplatin and vindesine, added substantial clinical benefit at a reasonable cost effectiveness of $15,000-$17,000 per year of life.[34,35] They hypothesized, given the magnitude of the benefit and the low cost of the drugs, that vinorelbine and cisplatin compared to best supportive care would give results similar to those of Jaakimainen and colleagues.[33]

Evans and colleagues used a decision analysis model to show that chemotherapy in combination with radiation and/or surgery for Stage IIIA or IIIB disease, in comparison to treatment without chemotherapy would improve survival at a cost of $3,348 to $14,958 Canadian per year of life saved.[36] The model was robust, in that it showed benefit at a reasonable cost under all situations of reasonable clinical efficacy. Although the economic impact on the province or nation would be large, the chemotherapy treatments fit existing monetary guidelines for use.[37,38]

Goodwin and colleagues have examined alternating and conventional chemotherapy for small cell lung cancer and found that the additional cost of the alternating therapy was partially offset by the enhanced efficacy.[39] Subsequent trials showed little advantage for alternating treatment, so this is not currently an issue.

*Gastrointestinal Cancer*

Glimelius and colleagues studied a mixed cohort of patients with various GI cancers randomized to first line chemotherapy vs. best supportive care that could include later chemotherapy for symptom control.[40] For the whole group, chemotherapy enhanced survival by about 5 months at a cost of about $20,000 per year of life gained, within accepted bounds.[27] For subsets of types of cancer, such as gastric cancer, the treatment was effective at a reasonable cost. For most other subsets, the patient numbers were too small to draw meaningful conclusions about either clinical effect or cost-effectiveness.

*Prostate Cancer*

In the only available analysis, mitoxantrone added substantial clinical benefit in terms of pain relief and symptom control but did not alter survival when compared to prednisone alone.[41] Although initial drug costs were higher, total disease costs were lower in the group that received mitoxantrone as initial treatment, established that good chemotherapy palliation could be accomplished at no additional cost to society.[42]

*Breast Cancer*

There are no reported studies on the effectiveness or cost effectiveness of chemotherapy for metastatic breast cancer compared to best supportive care. In the reported data, hospitalization accounts for the majority of costs, while chemotherapy has been a relatively trivial cost.[43] In the only available study of comparative treatment, Hillner et al compared best standard chemotherapy to high

dose chemotherapy with a stem cell transplant.[44] High dose chemotherapy added about six months at a cost effectiveness ratio of $116,000 per year of life gained. Although not routinely considered palliative care, HDC is commonly used for incurable metastatic disease, and in the one randomized controlled trial doubled overall survival from 10.4 to 20.8 months although it did not appear to produce long term survival plateau.[45]

*Other Diseases*

Chemotherapy for acute myelogenous leukemia, compared to supportive care and certain death, cost more. But the survival benefit 48% versus 21% at 5 years was sufficient to offset higher costs of treatment and make the cost-effectiveness ratio about $18,000/LY.[46]

**Table 3**. Chemotherapy vs. Best supportive care or alternative treatments.

| *Topic* | *Conclusion* | *Author* |
|---|---|---|
| *Lung cancer* | | |
| Chemotherapy vs. best supportive care in non-small cell lung cancer | Chemotherapy gained 8-13 weeks compared to best supportive care. Chemotherapy generally saved money for the province of Ontario, from a savings of $8,000 Can to additional cost of $20,000 depending on assumptions. | Jaakimainen [33] |
| Combined modality including chemotherapy vs. Radiation or surgery for Stage III non-small cell lung cancer | Chemotherapy in combination with radiation or surgery adds clinical benefit; for chemotherapy plus radiation one and five-year survival is increased from 40 to 54% and 6 to 17%, for instance. The addition of chemotherapy for IIIA patients added cost of $$15,866, and addition of chemotherapy to IIIB patients added $8,912. The cost year of life gained was well within accepted bounds at $3,348 to $14,958 Canadian. | Evans [37,38,46,47] |
| Alternating chemotherapy for small cell lung cancer | The alternating chemotherapy arm cost more, but because it was more effective, the marginal cost effectiveness was only $4,560/LY. | Goodwin [39] |

**Table 3**. Continued.

| *Topic* | *Conclusion* | *Author* |
|---|---|---|
| *Gastrointestinal cancer* | Chemotherapy added 5 months median survival if given early rather than late, with symptom palliation for 4 months. The additional cost of about $20,000/life year was within accepted bounds. | Glimelius [40] |
| Chemotherapy vs. Best supportive care followed by chemotherapy for GI cancer patients | | |
| *Prostate cancer* | Mitoxantrone did not improve survival, but improved quality of life as measured by several indices, and the mitoxantrone strategy cost less than prednisone supportive care. | Tannock [41] Bloomfield [48,49, submitted] |
| Palliative chemotherapy with mitoxantrone plus prednison vs. prednisone | | |
| *Breast cancer* | High dose chemotherapy added 6 months at a cost of $58,000, or $116,000/LY; this is palliative care as this treatment has not been shown to be curative. | Hillner [44] |
| High dose chemotherapy for limited metastatic disease vs. standard chemotherapy | | |
| *Other* | Chemotherapy, compared to supportive care, added additional cost but the cost effectiveness was $18,000/LY, within acceptable limits. | Welch and Larson [46] |
| Acute myelogenous leukemia | | |

## Site of Service

There are a limited number of studies available. (Table 4) Narcotic infusions at home had higher drug equipment, and nursing costs, but total costs were lower due to lesser hospital costs.[50] Outpatient administration of chemotherapy was less expensive than inpatient administration.[51] There is no only one study that compares home chemotherapy to outpatient chemotherapy.[52] The program was well-accepted with only two of 424 patients electing to discontinue home treatment. It was safe, with no major complication. The average cost was $50 compared to $116 in hospital, with equal total costs.

**Table 4.** Site of service.

| *Topic* | *Conclusion* | *Author* |
|---|---|---|
| Narcotics | Narcotics at home per diem costs were higher for home patients, but total costs were lower with equivalent palliation | Ferris [50] |
| Inpatient or outpatient chemotherapy | Outpatient administration was less expensive, $184 vs. 223 in US$. | Wodinsky [51] |
| Home or inpatient/clinic chemotherapy | Home chemotherapy was safe, well accepted, and cost less per treatment | Lowenthal [52] |

## Changes in Process or Structure of Care

Changes in disease management have shown some dramatic improvements but the data may be proprietary and not available. For instance, coordinated disease management by an expert team expanded home care services for AIDS patients by 600% but decreased total costs by nearly 50% (unpublished data, First Boston Corporation.) Similar results were seen in the disease management of congestive heart failure.

For terminally ill cancer patients, coordinated care offers many advantages. There is a long standing model in the Medicare Hospice Benefit, with nurse coordination, team management, easy access to low per diem hospital beds for respite or temporary care, and expanded drug coverage.[53,54] An English trial of adding a nurse coordinator for terminally ill patients did not change any disease outcomes; patients still died, and most still had some unrelieved symptoms, but patient and family satisfaction was helped slightly.[55] More striking, however, was that total costs were reduced from £8814 to £4414 for a cost savings of 41% in almost all conditions.[56] As in the AIDS experience, the savings came from decreased hospital days, even as home visits increased.

Allowing patients to die at home, consistent with their wishes, has become a worthy goal of palliative medicine.[57] Making nursing care available was associated with more patients dying at home.[58]

A system wide intervention on pain management that included enhanced institutional education programs, a consultative team, and a pain resource center appeared to decrease admissions and re-admissions for pain control.[59] Although the study was not randomized, and could not account for other significant changes such as the growth of managed care with restricted admission policies, the conclusion must be that this is better pain management, better medical care, and probably saves money.

An educational ethics program in the intensive care unit that addressed the issues of patient choice about dying, and the ethics of futile care, was associated with a decline in total costs. Again, the rapidly changing health care system could account for some of the change, but more ethically based care that valued the perspective of the patient caused no increased costs.[60]

Clinical practice guidelines for standard supportive care appear to have decreased costs, although formal data have not been published (reviewed by Smith [54]). As above, standardization of care has made important improvements in the process and costs of care even if not the outcomes. Clinical pathways for the surgical management of breast and lung cancer have improved results and lowered costs.[61]

**Table 5.** Process or Structural Changes in Care.

| *Topic* | *Conclusion* | *Author* |
|---|---|---|
| Reducing uncontrolled pain admissions | A system wide intervention of focus on pain management, a supportive care consultation team, and making a pain resource center. This was associated with a reduction in admissions from 255/5772 (4.4%) to 121/4076 (3.0%), at a projected cost savings of $2,719,245. | Grant R [59] |
| Coordinated nursing care manager for dying patients | A nurse coordinator did not improve symptoms of dying patients, but did reduce overall costs by 41%, from £4774 to £8034. This was accomplished by a reduction in hospital days from 40 to 24, along with an increase in nurse home visits from 15 to 38. Patient and family satisfaction were not worsened. | Raftery JP [56] |
| Clinical practice guidelines for supportive care: anti-emetics, treatment of febrile neutropenia, treatment of pain | A division changed practice to standardized oral anti-emetics, and once-daily ceftriaxone and gentamicin. Cost savings were estimated at $250,000 for each intervention, yearly. | Smith TJ [54,62,63] |

**Table 5.** Continued.

| *Topic* | *Conclusion* | *Author* |
|---|---|---|
| Clinical practice pathways for care on lung and breast cancer patients undergoing diagnostic workup and surgery | Pathways reduced variances in practice substantially, and generated cost savings. Care was thought to be improved. | Katterhagen G[61] |
| Acquired immune deficiency care | Up to a 50% reduction in total health care costs by reduced hospitalizations; home care visits increased by 600%. Financial details sketchy in this report, and data have not been published. | First Boston Report, 1995 (unpublished data) |
| Presence of nursing care for end of life | Nursing care availability allowed more patients to die at home consistent with the wishes of most patients. | McWhinney[58] |

## Hospice vs. Non-Hospice Care

Whether hospice improves care and saves money, or even improves care, cannot be settled from the available data.[54,64,65] This question has aroused considerable controversy even though hospice accounts for less than 1 percent of Medicare expenditures. The studies performed all have methodologic shortcomings which make firm conclusions impossible. In addition, hospice advocates tend to be quite vocal in their support of the hospice concept regardless of its impact on finances (much like advocates for any other type of medical care.) I have attempted to summarize the available data in Table 6.

The most methodologically sound study, a randomized controlled trial of hospice vs. standard care, is now 15 years old and will likely not be repeated.[66] This study did not show any significant difference in medical outcomes or costs for patients randomized to hospice or standard care. The shortcomings of the study are that it was done at a Veterans Administration Medical Center and therefore included mostly male blue-collar workers, not representative of most hospice patients. In addition, the hospice unit was newly formed and inexperienced and did not have routine referral lines (which probably would have precluded the study.) Also, the VAMC does not issue bills, so all costs were estimated using costs from nearby hospitals. The intervention was a special inpatient hospice unit with home care

services for 247 patients in the trial, done in the period 1979-82. Hospice did not improve or worsen quality of care by any measured benchmark (pain, ability to perform activities of daily living). Patients still used many hospital days, 48 for control, 51 for hospice, but more of the hospice patients were hospitalized on the hospice unit. There was no difference in diagnostic procedures. Total costs were $15,000 per patient, with no difference in the arms. This study has many flaws including the but provides the best evidence that - at least in some systems - hospice will not have dramatic cost savings.

**Table 6.** Hospice vs. Non-Hospice Care.

| *Topic* | *Conclusion* | *Author* |
|---|---|---|
| Randomized controlled trial of hospice vs. non-hospice care in Veterans Hospital | Hospice did not improve or worsen quality of care by any measured benchmark (pain, ability to perform activities of daily living.). There was no difference in diagnostic procedures. Total costs were $15,000 per patient, with no difference in the arms. | Kane RL [66] |
| Hospice election vs. Standard care, Medicare beneficiaries, 1992 | Medicare saved $1.65 for each $1 spent on hospice programs; most of the savings occur during the last month of life | Lewin-VHI[67] |
| Hospice election vs. Standard care, Medicare beneficiaries, 1988 | Medicare saved $1.26 for each $1 spent on hospice programs; most of the savings occur during the last month of life | Kidder [68] |
| Total costs from data bases | No significant difference in total costs from diagnosis to death, but significant cost savings of 39% for hospice patients who were in hospice over two weeks. | Brooks [60]and Smith-Staruch |
| Total disease management costs comparing those who elected hospice to those who did not | No difference or slightly higher costs among Medicare beneficiaries who elected hospice. Within the hospice period, average 27 days, costs were slightly lower for those who elected hospice. | Smith TJ [54] |

**Table 6.** Continued.

| *Topic* | *Conclusion* | *Author* |
|---|---|---|
| Home care | Home care provided by relatives is not much different ($4,563 for each three month period) than costs in a nursing home or similar setting. The sicker the patient became, the more the cost to the family regardless of diagnosis. Costs were lowest when the patient and care giver lived in the same household. | Given BA [71,72] |
| Matching resource use to the dying patient | Hospice patients more likely to receive more home nursing care, and spend less time in the hospital than conventional care patients. Conventional care was the least expensive when overall disease management costs were calculated, but hospital-based hospice ($2270) and home care hospice ($2657) were less expensive than conventional care ($6100) in the last month of life. | Aiken [69] |

The most recent data from a study funded by the National Hospice Organization suggests that hospice care can be cost-saving, as long as the health care and payment systems are aligned with incentives to provide good care at the least acceptable cost.[67] Using data from 1992 Medicare files, Lewin-VHI, Inc. found that those who elected hospice were less costly than cancer patients who did not elect hospice. For those who enrolled in the last month of life, typically over half of Medicare patients, Medicare saved $1.65 for each $1 spent. Those who elected hospice tended to use more resources in the months from diagnosis until about three months before death, so the total disease management savings were much smaller (if any).

In an earlier similar analysis of 1988 data, Kidder found that Medicare hospice would save $1.26 for each $1 spent.[68] As noted above, these savings were from prevention of hospitalizations in the last month of life. Total disease management costs, or costs in the year preceding death, were similar in those who elected hospice and those who did not.

Some authorities have voiced concern that hospice may actually not be saving total disease management costs, but just shifting them to sectors not captured by our current accounting systems. In our own study of Medicare hospice use in Virginia, total disease management costs were actually higher for those who eventually elected hospice. Those who elect hospice tend to be high socioeconomic class patients with resources to absorb more home care costs, more out of pocket drug

costs, etc. The data are consistent with an affluent group of patients using all the resources needed for treatment, then using hospice resources in addition. There is no data on whether the medically undeserved use hospice, will accept its philosophy, or how much those patients will cost the system.[54]

In one of the largest database studies with 12,000 patients at 40 centers, Aiken et al found that hospice patients were more likely to receive more home nursing care, and spend less time in the hospital than conventional care patients.[69] As noted, these patients were self-selected for hospice, so they may have used fewer or different resources anyway, and had more ability to absorb home care. Of the three models of care evaluated, conventional care was the least expensive when overall disease management costs were calculated, but hospital-based hospice ($2270) and home care hospice ($2657) were less expensive than conventional care ($6100) in the last month of life.

## Use of Advanced Directives

The use of advanced directives, such as "do not resuscitate" (DNR) orders, has been advocated to allow patients to make autonomous choices about their care at the end of life and possibly reduce costs by preventing futile care. However, as reviewed by Emanuel and Emanuel, there has been no cost savings associated either with the use of advanced directives or DNR orders.[64,73] (Table 7) These findings have been confirmed in the more recent SUPPORT study. [74]

**Table 7.** Use of Advanced Directives, Do Not Resuscitate Orders

| *Study* | *Conclusion* | *Author* |
|---|---|---|
| California Durable Power of Attorney for Health Care placed on chart | No effect on treatment charges, types of treatment, or health status. | Schneiderman [75,76] |
| DNR | Average of $57,334 for those without DNR orders, to $62,594 with those with DNR orders. | Maksoud [77] |
| Advanced directives in SUPPORT hospitals | No cost savings with advance directives. Prior to the SUPPORT intervention, there was a 23% reduction in cost associated with presence of advance directives, $21,284 with compared to $26,127 without. The intervention patients were more likely to have advance directives documented. Average cost was $24,178 for those without advanced directives, $28,017 for those with advanced directives on the intervention arm. | Teno [74] |

## Summary

The number of high quality health service research studies in care of the terminally ill patient is very limited. For some areas of care, such as coordination of care for the dying, the clinical benefit is not clear, but the cost-effectiveness evidence seems compelling enough to provide services. For others, such as the use of advanced directives or hospice care, the ethical and medical rationale is compelling, but the evidence of clinical benefit or better cost-effectiveness is limited.

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# RACIAL VARIATION IN CANCER CARE: A CASE STUDY OF PROSTATE CANCER

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## Introduction

There is convincing documentation of racial variation in the incidence and mortality of many cancers, particularly cancers of the breast, colon, lung, and prostate. [1,2] Racial differences are also reported in the clinical management of these cancers. [3,4] This phenomenon, that is, racial variations in the occurrence and treatment of disease, is not unique to cancers. Racial differences are found in incidence, patterns of care, and patient outcomes for many other diseases and conditions, e.g., cardiovascular and cerebrovascular disease.[5-8] Efforts to further document its existence would seem to be unwarranted.

The more interesting question, and one still in need of a definitive answer, is why these racial variations exist at all. The concern appears to be that the observed variations are primarily a consequence of racial discrimination.[9] This is an issue that must be resolved on a number of counts. Foremost, if racial discrimination is indeed the cause, this would constitute a socially unacceptable situation. More pragmatically, an understanding the reasons for the racial differences has importance for designing appropirate programs or interventions, whether focused on primary, secondary or tertiary prevention, to insure equal access to high quality health care.

As alternatives to racial discrimination, there are at least three possible explanations of the diagnostic and treatment variations for cancer. One of these explanations is socioeconomic status of which income is one of several dimensions. Racial differences in cancer incidence and survival, at least for some cancers, have been linked to socioeconomic status.[10-12] Socioeconomic status, particularly ability-to-pay, may account for the racial variations in patterns of care as well. Another potential explanation is a racial difference in clinical factors such as disease pathophysiology, stage at presentation or comorbid conditions that may be contraindications to some therapies or otherwise modify the choice of treatment. Third; there may be racial differences in patient preferences for therapy. Combinations of these explanations also may be involved. Again, it should be recognized that these explanations are broadly applicable to other diseases for which clear racial differences are observed such as occurs in cerebrovascular disease.[8]

In this chapter, we explore the current state of knowledge regarding racial differences in cancer-related health care, specifically as it relates to the treatment of prostate cancer. The strategy used to develop our understanding of racially-based patterns of care for prostate carcinoma is a template for explaining similar variations for other cancers and diseases. Because the literature emphasizes Blacks and Whites, this review, by necessity, reflects that focus, although wherever feasible, the situation for other racial/ethnic groups is presented. The fundamental concepts, though, are the same regardless of the specific racial or ethnic group considered. We begin with a discussion of race and its use in the health services literature, generally. Then, we put into perspective the situation for prostate cancer by describing racial differences in its epidemiology, particularly the survival rate (a.k.a. case fatality rate). Following this section, we review the most current evidence regarding the existence and various explanations of the observed racial disparities for prostate cancer treatment. We conclude with suggestions for future directions for research.

## Meaning and Implications of Race

Currently, race is regarded as a social concept that is a reflection of historical social and economic events and not a biological entity.[13-15] Indeed, some health researchers contend that race has no biological meaning and should be abandoned as a variable in analyses, particularly because the concept has been used in the past to bolster racist arguments of the purported inherent superiority of some racial groups.[16,17]

Historically, health services research has emphasized the socioeconomic aspect of race while potential biological aspects have been virtually ignored.[18,19] Although race is intimately intertwined with socioeconomic status (at least in the United States), attempts to "remove" this aspect of race in studies of racial variation in health and health services utilization have been unsatisfactory in many cases.

[20,21] That is, race continues to have a residual association with health status and health services utilization after income, education and other measures of socioeconomic status have been controlled. This finding suggests that race reflects factors in addition to socioeconomic status.

If, in the conduct of health research, we are to follow the advocated advice and define "race" as an indicator of skin color alone (i.e., racism), we need to be convinced that the effects of other factors are truly absent or controlled, including genetic profile or characteristics of the disease, income, education, and culture (or rather, patient preferences). As with any diagnosis by exclusion, it is essential to know that all other causes have, indeed, been excluded. The challenge for the health services researcher is to delineate and then "tease-out" or account for the relative explanatory influence of the several covariates of patient's race on the occurrence and treatment of cancer or any other disease for that matter. [22-24]

### *Implications of the Definition of Race*

Understanding the meaning of race as it is used in health services research is not an academic exercise that generates arcane knowledge. As mentioned previously, the reason(s) for racial differences in health services utilization has clear implications for policy development. For example, if race is an indicator of genetic proclivities for cancer development, this suggests policies that target high-risk racial groups for screening programs. If race is actually a proxy for economic factors, such as ability to pay for care, this suggests among other approaches the need for changes in content or eligibility for governmental health care financing programs, such as Medicaid. If race reflects a cultural orientation, e.g., patient preferences for certain therapies or misunderstandings about some therapies, this suggests educational strategies are required for physicians and patients so that patients may be fully informed about their treatment options. The fundamental objective in studying racial disparities in care is to insure the delivery of high quality care to all segments of the population.

## Race and the Clinical Course of Prostate Cancer

### *Epidemiology of Prostate Cancer*

Cancer continues to be the second cause of mortality in the United States for all racial/ethnic groups. Within this broad cause of death, a persistent and perhaps increasing racial/ethnic disparity exists in mortality rates for breast, colon, lung, and prostate cancer, especially between Blacks and Whites.[1]

Among males for the most recently available reporting period, prostate cancer was second only to lung cancer in incidence and mortality.[1] In 1992, the age-adjusted incidence rate for prostate cancer was 187.6 per 100,000 for Blacks versus 139.4 per 100,000 for Whites, yielding an overall rate ratio of 1.3. The age-adjusted mortality rate for prostate cancer for the 1988-92 period was 53.5 per

100,000 for Blacks versus 24.0 per 100,000 for Whites, a mortality rate ratio of 2.2. This is one of the largest ratios for site-specific cancer mortality.

Although for the incidence of prostate cancer, the experience of Blacks and Whites appears to be becoming more similar, the opposite is true for the mortality rate (Table 1). There is a clear increase in the relative and absolute difference in the age-adjusted mortality rate of Blacks vis-à-vis Whites. The relative survival rate shows a similar pattern to that for the mortality rate; that is, Blacks experienced a relative worsening in survival to that experienced by Whites over the 1974-90 period (Table 2). Adjusting for stage does not eliminate this racial disparity in relative survival. Indeed, the gap between Blacks and Whites in the relative survival rate demonstrates a broadening as the stage at presentation becomes more advanced. The stage-specific, relative survival rates for the 1983-90 period for Blacks and Whites, respectively, are 87.7 versus 94.7 for local disease, 69.3 versus 86.6 for regional disease, 22.7 versus 29.6 for distant disease, and 63.9 versus 76.5 for unstaged prostate cancer.

**Table 1.** Age-Adjusted Incidence and Mortality Rates for Prostate Cancer in Black and White Males, All SEER Program Sites.

| *Racial Group* | *Rate/100,000* | | | | |
|---|---|---|---|---|---|
| | 1973 | 1978 | 1983 | 1988 | 1991 |
| Incidence Rate | | | | | |
| Blacks | 106.4 | 116.5 | 133.5 | 146.0 | 209.6 |
| Whites | 62.3 | 73.2 | 83.4 | 104.4 | 159.2 |
| Black:White Ratio | 1.71 | 1.59 | 1.60 | 1.40 | 1.32 |
| Mortality Rate | | | | | |
| Blacks | 39.5 | 42.5 | 46.6 | 49.5 | 55.1 |
| Whites | 20.3 | 21.0 | 21.6 | 22.8 | 24.7 |
| Black:White Ratio | 1.95 | 2.02 | 2.16 | 2.17 | 2.23 |

Source: National Cancer Institute, 1994.

These racial differences in the mortality and relative survival for prostate cancer have particular interest in that such differences may reflect differences in the quality of therapeutic care received.

*Race and Patterns of Care for Prostate Cancer*

Even under casual examination, definite racial/ethnic differences are apparent in the therapeutic approaches utilized by prostate cancer patients (Table 3). Of particular interest, we find that Black patients are substantially more likely to

**Table 2.** Relative Survival Rates for Prostate Cancer in Black and White Males, All SEER Program Sites.

| *Racial Group* | *Relative Survival Rate* | | | |
|---|---|---|---|---|
| | 1974-6 | 1977-9 | 1980-2 | 1983-90 |
| Blacks | 58.0 | 62.1 | 64.4 | 66.4 |
| Whites | 67.7 | 71.9 | 74.3 | 81.3 |
| Black:White Ratio | 0.86 | 0.86 | 0.87 | 0.82 |

Source: National Cancer Institute, 1994.

receive hormonal therapy alone but less likely to undergo prostatectomy alone. This pattern of care appears to persist over time.

Such obvious differences in treatment generate two related questions. The first question is why are Blacks receiving what is often regarded as less aggressive therapy than Whites. The second question, which was alluded to previously, is whether this pattern of care contributes to either the higher mortality or lower relative survival rate that occurs among Blacks with prostate cancer.

**Table 3.** Racial/Ethnic Differences in Therapies for Prostate Cancer, Unadjusted for Sociodemographic and Clincal Factors. [4,25]

| *Therapy* | *Natl Cancer Data Base (1985-88)* | | | *CT Tumor Registry (1990)* | |
|---|---|---|---|---|---|
| | White (n=26,153) | Hispanic (n=881) | Black (n=2,687) | White (n=3,736) | Black (n=235) |
| TURP | 20.5 | 22.7 | 21.7 | 34.2 | 27.2 |
| Hormonal | 15.1 | 18.5 | 23.6 | 19.4 | 30.2 |
| Prostatectomy | 24.0 | 24.2 | 16.6 | 9.0 | 3.8 |
| Radiation | 29.0 | 21.7 | 23.7 | 11.7 | 14.5 |
| Other/Combinations | 11.4 | 12.8 | 14.3 | 14.8 | 13.1 |
| No Treatment | NA | NA | NA | 10.8 | 11.1 |

Sources: CANCER, Vol. 74, No. 5, 1994, p 1644; and Vol. 70, No. 8, 1992 p 2155. 

Evidence regarding the latter question comes from a sparse set of literature. From these few published reports, there is some support for the assertion that when treatment is similar, Blacks and Whites have similar outcomes. We find, for example, that among patients on standard oncology protocols where there is uniformity in evaluation and treatment, there is no racial difference in either overall survival or disease-free survival.[26] Likewise, in equal access systems where the care delivered to patients is purportedly irrespective of their race, no significant racial difference in overall survival is reported.[27,28] Unfortunately, the literature linking specific treatments with outcomes according to the patient's race does not consistently indicate a similarity of outcomes when similar treatment is provided. Thus, a recent study reports that time to recurrence of disease is shorter among the black vis-à-vis white patients who undergo radical prostatectomy.[29]

As for the former question, there is a relatively more extensive and consistent literature regarding the role of clinical and socioeconomic factors in explaining racial differences in types of therapy used by prostate cancer patients. There is essentially no literature on the importance of either patient preferences or the patient-physician interaction.

## Explaining the Racial Variation in Patterns of Prostate Cancer Care

*Role of Clinical Factors*

The clinical stage at the time of diagnosis of prostate cancer is one of the most potent determinants of therapy; it is also a potent prognostic indicator. For localized disease, preferred therapies include radical prostatectomy and external beam radiation, although expectant observation (that is, "watchful waiting") is often used as well.[30,31]

Regardless of the method of defining clinical stage, Blacks consistently present at a later stage of disease (Table 4). For example, using the staging criteria of the American Joint Committee on Cancer, Blacks are 1.65 times as likely as Whites to present with Stage IV disease while Hispanics are 1.35 times as likely as Whites to present at this stage: 29.3% and 24.0% for Blacks and Hispanics, respectively, versus 17.8% Whites.[4] Under the clinical staging criteria used by SEER (which approximates the Whitmore-Jewett staging criteria used by American Urological Association), in the Atlanta, Detroit and San Francisco metropolitan areas combined, Blacks are 1.72 times as likely as Whites to present with distal disease while patients of other racial/ethnic groups are only 1.14 times as likely as Whites to present with distal disease.[32] Not only is this phenomenon present nationally, a similar relationship is found across the geographically-diverse SEER sites. At both the Connecticut and Detroit SEER sites, Blacks are 1.6 times as likely as Whites to present with metastatic (distal) disease.[25,33] Correction for misclassification errors does not reduce or eliminate this difference.[34]

Even in equal access systems, Blacks present with a more advanced stage of prostate carcinoma, suggesting that ability to pay for care may not be an importance explanation of this occurrence. We find in the Department of Defense (DOD)

Table 4. Racial/Ethnic Differences in Clinical Stage of Prostate Cancer at Presentation, Selected Studies.

| *Source* | *Clinical Stage at Presentation* | | | |
|---|---|---|---|---|
| | Local | Regional | Distal | Unknown |
| National SEER 1984-91 [32] | | | | |
| Whites (n=78,431) | 58.5 | 16.5 | 13.4 | 11.7 |
| Blacks (n=8,632) | 52.6 | 12.4 | 23.0 | 12.0 |
| Other (n=5,036) | 51.9 | 13.1 | 15.0 | 20.0 |
| Detroit SEER 1973-91 [33] | | | | |
| Whites (n=22,632) | 65.1 | 7.3 | 16.0 | 11.6 |
| Blacks (n=7,781) | 56.7 | 7.5 | 25.4 | 10.4 |
| VA, Wayne County, MI 1973-92 [35] | | | | |
| Whites (n=358) | 57.3 | 9.5 | 19.0 | 14.2 |
| Blacks (n=383) | 53.5 | 8.9 | 25.1 | 12.5 |
| DOD Tumor Registry 1973-94 [27] | | | | |
| Whites (n=1,485) | 74.0 | 13.7 | 12.3 | NA |
| Blacks (n=121) | 57.9 | 15.7 | 26.4 | NA |



health care system Blacks are 2.1 times as likely as Whites to present with distal disease, a ratio of a greater magnitude than occurs in the non-federal health care sector.[27] In the Veterans Affairs health care system, the relative odds of presenting with distal disease for Blacks versus Whites is 1.3.[35] Although elevated, the difference is much lower than the 1.6 reported for Blacks vis-à-vis White prostate cancer patients at the Detroit, Michigan SEER site.[33]

Given the racial difference in stage at presentation, does adjustment for clinical stage eliminate the observed differences in types of therapies used? The published studies suggest with some consistency that stage at presentation is a primary

explanation of the racial difference in therapy (Table 5). Among patients in the Virginia Cancer Registry who have local or regional disease, Blacks are more likely than Whites to receive either no treatment or hormonal therapy but less likely to receive either surgery or radiation.[36] With adjustment for socioeconomic, clinical and health care system characteristics, there is no racial difference in either the likelihood of receiving any treatment versus no treatment or in receiving hormonal therapy or orchiectomy versus surgery or radiation. However, there remains a statistically significant racial difference in use of surgery versus radiation.

In Connecticut, among patients with local disease, there is no statistically significant difference in use of prostatectomy alone ($p=0.18$); radiation alone ($p=0.54$); or the combination of prostatectomy and radiation ($p=0.62$).[25] Similarly, for patients with metastatic disease, Blacks and Whites are equally likely to receive hormonal therapy: 60.8% for Blacks versus 57.6% for Whites ($p=0.61$). The only statistically significant racial difference is for use of prostatectomy alone for advanced disease, and Whites are more likely than Black patients to receive this therapy (4.7% versus 0%; $p<0.001$).[25]

National SEER data, however, indicate several important differences in therapy among patients with local/regional disease.[32] For patients less than 80 years of age, Blacks are less likely to receive radical prostatectomy than Whites; radiation is used more often among Blacks, particularly younger (50-59 years of age) Blacks. Whites are more likely to receive "definitive" or aggressive therapy (radical prostatectomy or radiation) than Blacks; this pattern is persistent over the1984-91 time period and holds for all age groups. Expectant observation is more common among Blacks at all time points; in 1991, for example, the proportion of Blacks versus Whites receiving this "therapeutic modality" is 12.5% versus 6.6%. These findings, though, are adjusted for only age and stage.

Using SEER data from those sites where the Black population is of sufficient size to yield statistically stable estimates (Atlanta, Detroit, Connecticut, and San Francisco), the unadjusted relative risk of receiving definitive or preferred therapy (i.e., radical prostatectomy or radiation) for Blacks with localized disease is 0.65 (95% Confidence limits=0.56, 0.75) [37]. With adjustment for clinical stage (Stage A versus B), tumor grade, age, geographic location and hospital factors, Blacks continue to have a statistically significant lower likelihood of receiving definitive therapy (relative risk=0.64; 95% CL=0.48, 0.86).

Similar findings are reported in the National Cancer Database of the Commission on Cancer for the years 1985, 1988 and 1990 [38]. For example, in 1990, 21% of Blacks with localized prostate cancer received radical prostatectomy versus 26.8% of Hispanics, 31.0% Whites and 23.6% of Asians. As with national SEER data, these results are unadjusted for factors other than stage. In an equal access system, without adjustment for clinical stage of disease, approximately twice as many Black as White patients received hormonal therapy: 20.7% versus 10.0%, and about 20% fewer received radiotherapy: 19.4% versus 24.5% ($p=0.008$).[27] However, within clinical stages, there is no racial difference in the types of therapy received.

Table 5. Racial/Ethnic Differences in Therapies for Localized Prostate Cancer, Selected Studies.

| *Source* | *Therapy* | | | | | |
|---|---|---|---|---|---|---|
| | TURP | Hormonal | Surgery | Radiation | Other | None |
| Virginia Cancer Registry, 1985-89 [36] | | | | | | |
| Whites (n=3,117) | NA | 12.4 | 17.3 | 28.9 | 5.4 | 36.0 |
| Blacks (n=751) | NA | 18.2 | 9.9 | 20.8 | 6.8 | 44.5 |
| Connecticut Tumor Registry (SEER) 1990 [25] | | | | | | |
| Whites (n=2,653) | 44.4 | 3.8 | 10.8 | 13.5 | 17.3 | 10.2 |
| Blacks (n=133) | 42.1 | 6.8 | 6.8 | 15.8 | 18.8 | 9.8 |
| DOD Tumor Registry 1973-94 [27] | | | | | | |
| Whites (n=1,099) | NA | 0.5 | 63.1 | 25.8 | 10.6 | |
| Blacks (n=70) | NA | 1.4 | 68.6 | 21.4 | 8.6 | |

Hormonal therapy includes orchiectomy in [36]; other therapy includes combinations of therapies; NA = not applicable to the study population.

Thus, Blacks consistently appear to present at a later clinical stage of prostate cancer than Whites. In turn, clinical stage at presentation appears to account for much, but not all, of the racial variation observed in the use of types of therapies for prostate cancer. Outside of equal access systems, when only stage is controlled in the analyses, a racial difference remains. In studies involving equal access systems where socioeconomic factors are minimal for all patients, no racial difference is found in use of therapies after controlling for clinical stage.

*Role of Socioeconomic Status*

How important is socioeconomic status as a determinant of therapy? We know that socioeconomic status does not appear to explain racial differences in the epidemiology of prostate cancer. The effect of socioeconomic status, whether measured by education or income, on prostate cancer incidence and mortality rates, is similar among Blacks and Whites.[10,11] Moreover, as previously discussed, socioeconomic status appears to have little or no explanatory power for understanding the clinical stage at which Blacks and Whites present. Blacks consistently present at a later clinical stage of disease even in health care systems where ability to pay for care is not in question.[27,35,39]

Given the general importance of socioeconomic status and, specifically, the ability to pay for care in gaining access to health care, it is reasonable to expect that socioeconomic status is an important determinant of therapy. However, a thoughtful review of the evidence from federal (i.e., equal access) and non-federal patterns of care suggests that ability-to-pay may have little or no role in explaining racial variations in the types of therapy for prostate cancer. Within the federal health care systems, either the Veterans Health Administration or Department of Defense medical centers, financial incentives for providing or withholding care are minimal. The patient, generally, is not responsible for the cost of the care received. Moreover, the physicians are salaried, having little financial incentive to either perform or not perform procedures. Care decisions, then, are driven primarily by the patient's need. Revisiting the published evidence from one of the few studies of prostate cancer involving an equal access system, we find patterns of care similar to those found in the non-federal health care sector.[27] This suggests that ability-to-pay has minimal influence on care patterns.

Moreover as previously noted, even in studies that control for socioeconomic status (as well as clinical stage) in the analysis, racial differences persist in type of therapy used.[36] This is an additional indication that ability-to-pay may have either a relatively less important or an indirect explanatory role in understanding racial variations in prostate cancer therapy.

Are there any plausible alternative explanations for these patterns of care other than socioeconomic status? It might be hypothesized that clinical factors in addition to stage of disease (such as comorbid conditions) account for the variation in care. At least one study reports that comorbidity is associated with both the

decision to treat local or regional prostate cancer and the type of treatment used.[36] Thus, the patient's comorbidity profile could possibly account for the similar patterns of racial variation in use of therapy that are found within and outside equal access health care systems. The hypothesis that differences exist in comorbidity profiles between black and white prostate cancer patients is a testable one and, perhaps, should be examined.

Also, ability-to-pay is just one dimension of socioeconomic status. Other dimensions of socioeconomic status, such as education or knowledge, may be worth exploring as possible additional factors that have a role in explaining the racial differences in prostate cancer therapy.

*Role of Patient-Physician Decision-making*

Neither racial variations in patient preferences, knowledge and beliefs nor the role of the patient's race in the patient-physician decision-making process have been thoroughly investigated as potential explanations of the observed racial differences in patterns of care. This may be due, in part, to the relative greater importance associated with clinical factors, particularly stage at presentation. And, this not to say that patient preferences should be ignored or that such preferences should be discounted in the choice of therapy.[40] The appropriate role of patient preferences in the selection of prostate cancer therapy is beyond the scope of this chapter. However, patient preferences as an explanation of racial variations in patterns of care for prostate cancer merits our attention.

Regarding racial variations in patient knowledge, attitudes or beliefs about prostate cancer therapy, recent investigations suggest that Blacks are less likely to see themselves at high risk of prostate cancer and may have a more pessimistic view of the impact of prostate cancer on quality of life and of the prognosis.[41-43] Such attitudes may indirectly account for the racial differences in the therapies used by influencing when in the natural history of this disease that black patients present. That is, because of their more negative views of prostate cancer, black patients may delay seeking care, resulting in a later stage at time of diagnosis.

Regarding physician-related knowledge, attitudes or beliefs in the selection of therapies for patients with prostate cancer, the evidence is limited and indirect. A recent study indicates that there is sufficient deviation from preferred practice patterns in clinical management of prostate cancer to warrant concern.[44] Specifically, 13% of practicing urologists would consider using hormonal therapy in patients under 70 years of age who have localized disease. Although this study focused on the association between patterns of care and the patient's age, it has relevance here because Blacks generally present at younger ages.

Another study examined the role of physician discretion in explaining racial differences in the use of various surgical procedures, including prostatectomy, among Massachusetts residents who had been hospitalized in 1988.[45] Prostatectomy was classified by an expert panel as a moderately discretionary procedure. In this study, the age- and sex-adjusted rate of use of prostatectomy was slightly lower (i.e., 7%) in Whites than Blacks; for other procedures classified as

moderately discretionary (carotid endarterectomy, cholecystectomy, and lumbar disk procedures), Whites were 27% to 300% more likely to use the procedure than Blacks. A similar level of racial variation is found among procedures classified as high- and low-discretion. Obviously, interpretation of these findings must be done cautiously because there is no adjustment for clinical or other factors that are important determinants of procedural used. However, one interpretation of these findings is that patients preference may be a relatively more important determinant of utilization of many therapies than the physician's opinion.

## Future Directions

Given that racial variation in the clinical stage at presentation primarily explains the observed differences in use of therapies, there are at least two compelling avenues for future investigations of racial differences in prostate cancer treatment. One is racial differences in disease pathophysiology and its implications for screening and early detection programs. A second important avenue for future research is the role of patient knowledge and beliefs in the use of screening programs. It also may be worthwhile to examine whether Blacks receive suboptimal care within treatment modalities [46], although Blacks and Whites appear to have a similar survival experience within these modalities after adjustment for clinical stage and other factors [27].

*Race and Aggressiveness of Disease*

One question that is being asked increasingly is whether Blacks experience a more aggressive form of prostate cancer.[47] Although far from conclusive, evidence is accumulating that lends some support to this conclusion. First of all, there is a long history of epidemiological studies that document a higher incidence and earlier onset of prostate cancer among Blacks.[31,48-51] Second, time to recurrence may be shorter in black than white prostate cancer patients despite similar treatment and clinical stage at presentation, although this is not a consistent finding.[26,29] In addition, premalignant lesions, i.e., latent prostate cancer are greater in volume among Blacks versus Whites.[52,53] A more systematic assessment of racial differences in the natural history of prostate cancer would appear warranted. If proven, this would argue for intensive screening programs that target younger black men.

*Race and Screening Programs*

Even if a more aggressive form of prostate cancer does not afflict Blacks, studies show consistently that Blacks present at a later clinical stage of disease than Whites even in equal access systems such the Veterans Health Administration and Department of Defense[27,35,39] Existing evidence, which is far from sufficient,

indicates that Blacks do not perceive themselves to be at high of risk which the epidemiology of prostate cancer clearly indicates they are. Moreover, Blacks may be delaying evaluation because of fears regarding disease prognosis.[41-43]

Here, the health beliefs model can be a useful guide for focusing investigations into the reasons for under-utilization of prostate cancer screening programs and, thereby, for the design of more effective programs. The health belief model, which has been validated for use in Black populations, operates on several premises.[54-56] Patients are assumed to act on medical advice or engage in health behaviors such as participating in screening programs based on perceived personal susceptibility to the disease, perceived seriousness of the disease, belief in the effectiveness of the recommended care or activity, and desire to regain or maintain health as balanced against perceived barriers to the care such as cost of care and level of satisfaction with previous health care encounters. Studies, then, could focus on one or more of these dimensions to identify those that are most explanatory of the observed racial differences.

## Summary

Prostate cancer is one of several cancers that affects U.S. racial and ethnic groups differently with Blacks experiencing a higher incidence and mortality rate than Whites. Observational studies indicate that black patients with prostate cancer are less likely to receive definitive therapy. This pattern of care appears to be attributable primarily to the later clinical stage of disease at presentation; socioeconomic considerations as such relate to access to care (e.g., ability to pay) appear to play a lesser role. Other patient related factors, for example, preferences for certain therapies, have not been well studied; consequently, their ability to explain racial variations in use of therapies for this disease is unclear. Potential areas for future research should focus on the reasons for the detection of the disease at a later clinical stage and, hence, with worse prognosis.

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# EVALUATING FOCUS GROUP DATA: BARRIERS TO SCREENING FOR PROSTATE CANCER PATIENTS

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## Introduction

There is no doubt that the quantitative sciences of mathematics and statistics have contributed enormously to the rapidly growing scientific knowledge in medicine. However, just as medicine combines the nonquantifiable art-of-care with the quantifiable science-of-medicine, health services research can profitably use non-mathematical data without sacrificing scientific practice. Health researchers used to reading tables full of t-tests and p-values may feel skeptical of the scientific validity of qualitative research. The purpose of this paper is to show how qualitative research using focus groups (FG) and content analysis can be use to advance knowledge about the attitudes of potential cancer patients. The focus of this study is demonstrating the proper way to use focus groups in research on prostate cancer (PC). An investigation the attitudes of selected at-risk elderly men toward a particular care-seeking behavior, having a digital rectal exam (DRE), is used as an illustration of the qualitative methodology. Throughout the paper, the methodological consideration, relating to research techniques behind the data are featured to clarify the methodology and reinforce the scientific value of the results.

The detection and treatment of PC presents a multitude of challenges to clinicians and researchers, and relevant issues make it an ideal disease for using FGs. PC has a long latent period in which it remains asymptomatic. Screening

programs are associated with higher rates of early diagnosis of PC. PC is more prevalent among black men as well as men of lower socioeconomic status (SES) for whom it is usually detected and treated at later clinical burden, that is, at a higher stage and grade [1]. The reasons for late detection among these groups, whether biological, social, or some combination, remains unresolved [2,3]. It is important to understand how these most vulnerable populations weigh the risks, severity, costs, benefits of pursuing preventive screening for PC. Such groups can be difficult to locate and a challenge to have discuss health concerns, especially one involving a painful screening technique, the DRE, and one whose treatment outcomes can impact patients' life expectancy and quality of life.

## Methodological Issues in Using Focus Group Data

While qualitative research does not generate statistically valid statistics for hypothesis testing and can not be generalized beyond the population under investigation, it has a number of advantages over standard survey data. It generates detailed responses in an open-ended format, allowing maximum flexibility for respondents to express themselves. Sensitive issues can be explored in a less threatening environment. The possibility for the discovery of new issues is also in the forefront, which makes qualitative research particularly useful in the earliest stages of an investigation. In this respect, qualitative research most closely resembles case-series epidemiological studies.

There are certain considerations that are particularly important in using FGs for medical research. Themost important of these issues are the setting of the interviews, the differences of FG versus individual interviews, and the generalizability of the findings. The most important considerations about the setting of the FG interview are the size and composition of the groups [4]. The size of the group should be governed by two considerations. First, it should not be so large as to preclude adequate participation by the members. Second, it should not be so small that it fails to provide substantially greater coverage than that of an interview with one person. Research has suggested that about eight is the best size to achieve this purpose, and the groups here are slightly smaller than this ideal, with the mean group size being around five, the median is four and the range from two to seventeen (Table 2).

With regard to group composition, it appears that the more socially and intellectually homogenous the group, the more productive its reports. This is due do the perceived disparities in social status which can lead to inhibition on the part of those of lower standing. Experience to date seems to indicate that the important consideration is homogeneity in education level. Fortunately, in part as a result of smaller group size, homogeneous composition of groups by education and race was largely achieved (Table 2).

Social processes at work in a group make a group interview different than individual one [4]. The advantages of group interviews include the release of

inhibitions, the widening range of response to questions, and activation of forgotten details. Inhibitions are released primarily due to less inhibited members of the groups broaching subjects which allow others to do the same; an example of this in a similar group setting are the numerous successful 12-step programs patterned on the successful format of Alcoholic Anonymous. Groups permit a range of responses to the same issue in the same way an open-ended question does on a conventional survey. This is particularly helpful in searching for unexpected concerns to questions, which is one of the primary goals of this research. Groups tend to cause the activation of forgotten details when one member reminds another of a certain relevant set of details long forgotten. Also, the give-and-take nature of a focus group allows responders to offer ideas when they come to mind and add them in the natural flow of conversation.

Conversely, the corresponding disadvantages of group interviews include the tendency to focus on the dynamics of the discussion to the exclusion of the content of the discussion, the "leader effect", and the possibly intimidating effect of venturing an opinion in front of others. Each of these problems can be addressed by skillful handling on the part of interviewers, something taken into account during the conduct of the FGs, as discussed below.

There is a concern about the relative generalizablity of the results from non-random samples in FGs. All of the participants in the FGs are from the state of Louisiana, in the area surrounding Louisiana State University. The members of the groups are not chosen randomly from a population to which the results of the analysis can be statistically generalized, and it was in this sense a "convenience sample". However, the scare quotes are included precisely because it was quite challenging, and not at all convenient to find some of the individuals from various social groups known to be importantly at higher risk for PC. Care must taken not to assume that these individuals' opinions can stand for the opinions of others as in a representative sample. Rather, they are being asked to state their opinions about a difficult subject area in a non-threatening environment, often one in which they spend much of their time. To the extent that they represent some segment of the at-risk population, their opinions will help in understanding the thought processes of others like them in relevant ways. This points to reasons why FGs are particularly useful at the beginning of a study in an area: they allow for exploration of an issue when researchers are still in the dark about an area. It is crucial that physicians and health systems concerned about offering programs for early detection of PC understand these concerns, and FGs offer a unique way to do this. The loss in generalizability is compensated by the gain in detailed understanding.

## Data

*Background of the Focus Group Effort*

The FGs were conducted with the primary intent of gathering information about the general health prevention behaviors and the PC screening attitudes and practices of

older American men. There was an emphasis on community relations in the contacting of groups for study. From the start of the study, considerable time and effort was spent on developing contacts with key people in the community, particularly black men. The contact effort proved to be onerous, with a great deal of resistance found from the most at-risk populations, indicating the difficulty in obtaining their attitudes and knowledge which was at the heart of the study. This also indicates how FGs can be useful in learning about specific hard-to-reach populations. In a typical random-sample survey with non-response, the most difficult to reach individuals may be the group of primary interest.

The method of contact moved from mailings and phone calls to direct contact such as visits to work locations, community agencies, churches, and civic groups. Usually, such visits were made to places where the researchers had established previous contact in some way, either through a personal acquaintance or a professional relationship. Also, the most direct method was street-intercept, in which researchers showed up unannounced at a location that was known to have a target population of interest and seek volunteers for a focus group. This method had some important success in contacting at-risk individuals. The key factor in all of these contacts seems to be identifying the key individual(s) who possess both interest and influence in the study. This approach again stands in contrast to a typical survey where the idea of finding "key individuals" would be unthinkable.

## Methods

*Conduct of the Focus Groups*

The empirical data described here are transcriptions of recordings from 32 focus group interviews with men either at-risk for PC or recovering from treatment for PC in Louisiana between the months of March and June in 1994. The FGs were recorded on audiotape, with participant consent, the tapes were transcribed into hard copy documents, and the hard copy documents were converted into computer-analyzable text.

Each focus group leader was provided with a Topic Guide based upon a combination of the experience of doctors with PC patient care, a review of the PC literature, and general focus group guidelines. Two Research Associates received training--consisting of a lecture, videotape viewing, and field experience in moderating FGs from a behavioral scientist with experience in focus group research.

After completing a demonstration group, two supervised groups, and a focus group moderated and recorded by Research Associates, the process was evaluated prior to moving forward. This resulted in several changes. First, a new Topic Guide was developed which was structured with a sequence of questions from the general to the specific. Moderators were to try and follow the new format rather closely, with slight deviations as necessary to insure conversation flow. One of the

virtues, of these FGs is the consistency of the content asked across the groups. Also, a format to report the FGs was developed which described the type of group and its general composition.

Each transcript contains a cover page, status report, summary report, and an evaluation form. The cover page is a check list of the other various components, and it provides explanations of any unusual circumstances involving a component, such as missing information. The status report contains demographic information on each focus group. It gives information about the number of group participants, their ages, their races, their education level, and their employment status (Tables 1 - 2). The evaluation form is adapted from a handbook for focus group research [5]. The form records whether a focus group meets the informational needs and the desired criteria established for the study. All of these are done to help insure the scientific integrity of the research effort.

**Table 1.** Focus Group Demographics, Overall.

| | | |
|---|---|---|
| *Number of groups* | | 32 |
| Age | Mean & Standard Deviation | 60.9 ± 12.6 |
| | Range | 39-95 |
| | | Percent |
| Education | Less than High School | 2 |
| | Some High School | 31 |
| | High School Graduate/GED | 28 |
| | More than HS | 40 |
| Race | White | 49 |
| | African-American | 51 |
| Employment | Yes | 42 |
| | No, Not Retired | 14 |
| | No, Retired | 44 |

*Questionnaire Structure*

The questionnaire was organized using the Health Belief Model (HBM), the most widely studied social-psychological model of care-seeking behavior, as a guideline [6-8]. In the HBM, a variety of social, demographic and structural factors are proposed to influence behavior through their effects on beliefs about different

**Table 2**. Focus Group Size and Composition by Race and Education.

| | | *Frequency* |
|---|---|---|
| Group Size | 2 | 2 |
| | 3 | 11 |
| | 4 | 4 |
| | 5 | 5 |
| | 6 | 2 |
| | 7 | 5 |
| | 8+ | 3 |
| | Unknown | 1 |
| Group Race | All White | 9 |
| | All Black | 10 |
| | Mixed* | 7 |
| | Unknown | 6 |
| Group Education | | |
| <HS Graduate | All | 9 |
| | White | 3 |
| | Black | 2 |
| | Mixed | 3 |
| | Race Unknown | 1 |
| HS Graduate | All | 9 |
| | White | 3 |
| | Black | 3 |
| | Mixed | 2 |
| | Race Unknown | 1 |
| >HS Graduate | All | 7 |
| | White | 3 |
| | Black | 4 |
| | Mixed | 0 |
| | Race Unknown | 0 |
| Level Unknown | All | 7 |
| | White | 0 |
| | Black | 2 |
| | Race Unknown | 4 |

*It is assumed that even one member of another race could change the conversational rapport in the group.
**The educational level of each member of the group is summed and divided by the number of members of the group. Most groups had uniform education levels across its members.

aspects of health decisions (Figure 1). There are four constructs of the HBM: perceived severity of condition, perceived susceptibility to condition, perceived benefits and costs of taking action, and cues to taking action. The principles of the model can be explained in the following way. First, one should account for the individual's state of readiness to take action, which is determined by both the perceived susceptibility to the particular illness and the perceived severity of the consequences of contracting the illness. Second, consideration is given to the individual's evaluation of the health behavior in terms of its feasibility and efficacy (i.e. it's benefits) as considered against its physical, financial, and other barriers to action (i.e. it's costs). Third, a cue to action has to trigger the activation of the behavior. The source of these cues can be either internal or external to the individual; internal cues are the development of and awareness to the symptoms of disease, while external cues are information sources such as spouses, friends, and the mass media. Given the overlap of the HBM with the other care-seeking models [9], this series of questions will provide specific content to the concerns of men at risk for PC.

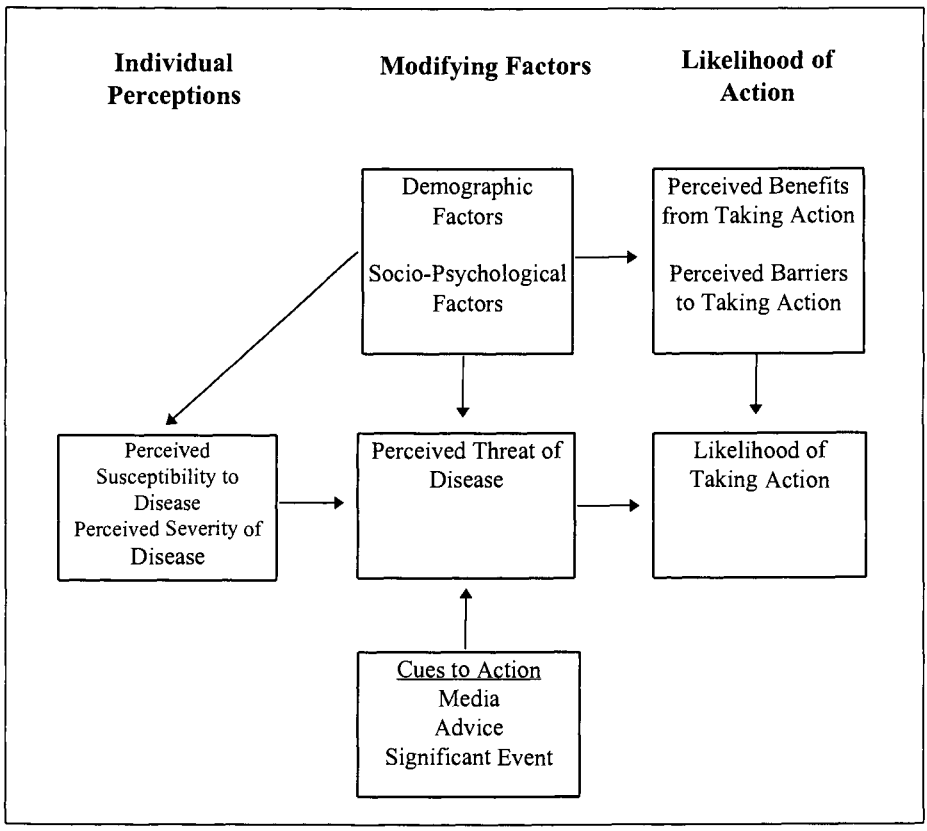


**Figure 1.** The Health Belief Model.

*Analytic Approach*

A computer-based content analysis was performed on the transcripts. The content analysis is carried out keeping in mind the structure of the questions asked of the participants, namely using implications from the HBM to organize the collected responses into categories. A computer-based text-retrieval program, ZyIndex, was used to conduct the content analysis of the transcripts. In conducting an electronic content analysis using the text-retrieval search of the transcripts, a concept is developed represented by combinations of words selected to represent a topic of interest. The concept is used to direct the information search to the relevant areas of the transcripts. Once an area is located, a careful reading is done of that section of the transcript and notes are taken discussing the topic. For the area explored, themes are identified and coded into tables, the tables are discussed, and some archtypical quotations from the transcripts are given to add specific, concrete detail to the summarizing tables and their accompanying discussion. This last step adds more vivid detail to the general comments, an important supplement to the quantitative analysis which permits respondents to offer opinions in their own words rather than being confined to those offered by a questionnaire. This again illustrates a virtue of qualitative research in providing specific detail about an area under investigation.

*Concept Studied: Digital Rectal Exams*

The illustrative concept explored was the digital rectal exam (DRE), an important area of concern for men considering seeking preventive medical care for the early detection of PC. A crucial element in the timing of detection is how, potential patients, particularly high risk patients, make the decision to visit the doctor for a checkup, since it is during such visits that the screening DRE could occur. There is a potential portion of a general physical exam related to the early detection of asymptomatic PC, namely the digital rectal exam (DRE). The exam is uncomfortable, at best, which leads many men to avoid it, even if they have a physical exam. To search for discussions of this topic in the transcripts, the following four cognate terms were entered as a concept into the text-retrieval program: DRE, digital exam, rectal exam., and prostate exam. One hundred three instances of context-relevant discussions were located; they are discussed below (Table 3).

## Results

*Group Demographics*

In order to clearly specify the population to which the results apply, since they are not statistically generalizable to a larger population, it is important to include a description of the demographic composition of the group. The focus of this study

**Table 3**. Digital Rectal Exams, Attitudes and Reasons.

| *Attitude* | *Reason* | | *Number* |
|---|---|---|---|
| Negative | | | 65 |
| | Painful or Uncomfortable | | 27 |
| | Social Discomfort | | 34 |
| | | Embarassment | 10 |
| | | Joking | 11 |
| | | Opposite Gender MD | 7 |
| | | Reputation of Exam | 6 |
| | Skepticism of Value | | 4 |
| Neutral | | | 27 |
| | Necessary | | 15 |
| | Used to It | | 10 |
| | MD Scheduling | | 2 |
| Positive | | | 11 |
| | Good Check | | 11 |
| Confusion | | | 7 |
| | Computer | | 2 |
| | Sigmoidoscope | | 3 |
| Total | | | 103 |

were men in lower SES categories and black men, two groups known to be at increased risk of late-stage PC diagnosis.

Overall, ages ranged from 39 to 95, with a mean of 61 (Table 1), well within the age ranges usually noted for prostate cancer patients. Sixty percent of the men have a high school education level or less, and they are split evenly between blacks and whites. Focus group size ranged between 2 and 17, with the mode being 3 (which was the size of 11 of the 32 groups); there was a rather even distribution across group size by race and education (Table 2). The groups were divided by racial composition roughly evenly into all white (9 groups), all black (10 groups), and mixed (7 groups). Similarly, the education level of groups was evenly divided into the four categories.

*Attitudes Toward DREs*

Men's attitudes toward this exam ranged from strongly negative through weakly positive, depending primarily upon two factors--their immediate reaction to

undergoing the procedure versus their assessment of the medical value of the exam. These two factors correspond roughly to the HBMs areas of "barriers" to taking action and the perceived "benefits" from taking the action. There was also several instances of confusion about what a DRE was among the men, indicating some had opinions about it based on misconceptions.

The overall response to the DRE was negative, with 65 responses being negative in some way, 27 being neutral, and 11 being positive. The negative responses, which focused largely on the immediate reaction to having the exam performed, divided into four areas: physical discomfort, social discomfort, reputation of the exam, and skepticism about the value of the exam. The neutral responses, while accepting that the exam was an unpleasant experience, focused on the fact that it was a necessary part of a checkup that they had become used to having done. The infrequent positive responses focused even more on the idea that the exam was a good preventive check, not even mentioning any discomfort they felt during the exam. The most usual response when asked about their attitude toward the DRE was immediate: it is uncomfortable and even painful:

> FACILITATOR: How does that make you all feel since everyone's had it? Just general feelings. Let's hear it.
> VOICE: Uncomfortable as hell.

And, even more vividly:

> FACILITATOR: How do you feel about having the rectum checked, a rectal exam? How do you think men feel about that?
> VOICE: Are you talking about where they ram their finger up in you?
> FACILITATOR: That one.
> VOICE: Well, it always hurt...

A reaction that was equal in frequency to the straightforward dislike of the physical discomfort involved in the DRE was the social or psychological response to it. Men are just as bothered by the stigma associated with the exam as they are about the pain of the exam itself. A nickname for the exam came up repeatedly -- men refer to it as "the finger wave." Many of them covered their embarrassment about it with jokes and nervous humor when the subject was brought up, often making comments about looking for a doctor with small hands, There were regular occasions of laughter, joking, and embarrassed comment recorded when the subject of the DRE came up. For example, one man said, "I felt something going the wrong way on a one way street." Other examples were:

> FACILITATOR: ... Has everyone had that exam?
> (Laughter)
> So ho, do you all feel about the exam itself?
> (Laughter)

VOICE: It always tickles him.
(Laughter)

VOICE: I'm going to keep my pants up when I come in here. I know what this is about.
(Laughter)
FACILITATOR A: What did you say about keeping your pants up?
VOICE: Damn right. I'm going to keep my pants up. I know about this, what you all are talking about. FACILITATOR A: What are we talking about?
VOICE: Prostate cancer.
FACILITATOR A: And how does the doctor check for that?
VOICE: Don't worry about it.
(Laughter)

FACILITATOR A: For those of you all that have had it, tell me how you feel about that exam. What are your thoughts about it?
(Laughter)
FACILITATOR A: What are your thoughts? I hear laughter and --
VOICE: How do you feel about a female exam?

This last reaction, comparing the exam to the gynecological exam for women, lead, into another area of psychological discomfort: female physicians performing the DRE. It is clear that some men in this cohort have not separated this exam as a medical check from sexuality. These men are extremely uncomfortable with the idea of the woman performing this exam:

FACILITATOR: Who else was going to say something? I heard laughter from this little domino table here.
VOICE: I just said I had a lady doctor who did it like that.
FACILITATOR: A lady doctor? Did that make a difference?
VOICE: To me it was embarrassing.
FACILITATOR A: Do you think you would have been uncomfortable if the doctor was a person of the opposite sex, if the doctor was a female?
VOICE: That was my problem. See, it really wasn't that bad but all my doctors up until then had been male doctors and I imagine there were probably a half a dozen different ones come in..
FACILITATOR A: You said that --
VOICE: I just said I think that's what was kind of embarrassing, because she was a woman doctor, not because of what she was doing but I had just never had a woman doctor do that before.
FACILFTATOR A: Check you before?
VOICE: Right.
FACILITATOR A: You were going to say something?

VOICE: Yeah, not that I have anything against women doctors but if it had been a woman doctor, I don't
think I would have had the exam.

One additional area of social stigmatization is the reputation of the exam. In the social circles in which many of these men spend their time, there are regular "horror stories" about the DRE. This is the form in which many of these men first hear about the exam before they ever have the exam themselves. They feel terrified of the exam, although they often find it's not as bad as they heard:

VOICE: It's kind of like a dog barking and its bite. I heard so much of it years ago that I dreaded it when I first went. It... but now it's not quite as --
VOICE: It's kind of routine.
VOICE: I can psych myself out and walk in.
FACILITATOR: So what types of things did you hear way back when about the exam?
VOICE: That it hurt.
VOICE: The first thing I heard is that when you bend over that table the man sticks his finger in, you want to pick up the table and walk. Well, I didn't think I would start walking but it was a new experience.

The final reason men give for a negative attitude toward the DRE is that they are skeptical about its value. In the HBM, this would be a low score for the assessment of the benefits from having this exam done.

Moving from the negative through the neutral to the positive assessments of the exam, there were three ways the DRE was discussed in a neutral way and one way it was discussed in a positive light. Many men found the exam to be "necessary" (15 instances) or said they were simply "used to" having it done (10 instances) so that it did not bother them very much any longer. Often, such comments were made in the midst of a discussion by others about how uncomfortable they found the exam, and this seemed to be a way to balance the comments of others. It also illustrates, as suggested by the HBM, the effect of decreasing the barriers to the carrying out of a preventive behavior. This seems to indicate the "transition" from the negative focus on the physical and psychological unpleasantness of the DRE to the positive focus on the long-term, preventive benefits from having the exam. There were only 11 instances of the DRE being judged in a primarily positive light, all of which discussed its value as a "good check."

There is a noticeable shift in attitude about having a DRE as men express increasingly positive assessments of it. Rather than focus on the pain, embarrassment, and fear about the exam itself which causes the most negative responses, men begin to become "used to" the exam with regular checks and they begin to think about the value of early detection. With increasing experience, men increase their assessment of the benefits of the exam and decrease their assessment of the barriers to having the exam done.

## Discussion

This study used focus group interviews with men in high-risk groups for PC, used the theoretical background of the HBM, and used a text-retrieval software package to conduct a content analysis to understand men's attitudes about getting a DRE as a check for PC. Various concerns about the use of qualitative data were addressed at each step of the study, including active contact of desired at-risk individuals, careful training of interviewers, creation of educationally and racially homogenous groups, conduct of groups according to published standards, reporting of the study population demographics, and clear explanation for how the content analysis was performed. Each of these helped insure the scientific validity of the results while allowing for full gain from the unique character of the qualitative data in providing a detailed picture of men's attitudes toward having a DRE.

The substantive findings were as follows. Men's opinions about the DRE are primarily negative due to an enormous barrier: it is physically painful and psychologically distressing. These barriers far outveigh considerations about the benefits to be gained for most men, although a few men are skeptical about the value of the exam. A smaller number of men express neutral attitudes about the exam. They focus on the benefits derived from the knowledge gained from such an exam, describing it as "necessary". Also, they tend to view the exam as less painful and intrusive, describing themselves as "used to it". Such men perceive some benefits of the exam and have dramatically reduced the barriers so many other men note. Finally, there 's a smaller group of men who are positive about the exam, primarily due to its benefits in early detection of disease, considering the exam to be a "good check". An important misunderstanding on the part of some men is mistaking the DRE with a sigmoidoscopy, an invasive screening procedure for colon cancer which is also very uncomfortable. It is important that such misconceptions be eliminated to alleviate unnecessary fear.

These results indicate that in order to increase men's willingness to undergo DRE, the barriers relating to physical and psychological pain must be reduced for most men and the medical importance of the exam emphasized. While little can be done to reduce the physical discomfort involved, more can be done to reduce the psychological barriers. Certainly, any misapprehensions about the exam, such as confusions with sigmoidoscopy, must be eliminated. Further, the exam must be performed in a relaxed, clearly medical manner to remove any sexual overtones from the encounter. Such psychological considerations are especially important for men just beginning to enter the at-risk period in life around 50, as the exaggerated negative reputation of the exam will precede it, and as many men have not become accommodated to the experience. All of these clinical skills are crucial in decreasing the current barriers and increasing the benefits in the eyes of these men toward DREs.

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# PROMOTING INFORMED DECISION MAKING: HORMONE REPLACEMENT THERAPY

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## Introduction

*Why is Hormonal Replacement Therapy a Cancer Issue?*

Although most gynecologists recognize the importance of discussing hormonal replacement therapy (HRT) with their patients, the controversies regarding the association between HRT and cancers, the questions about HRT use in women with a high risk of breast cancer, and the increasing number of women with breast cancer and menopausal symptoms make HRT a significant cancer issue. The scope is immense and growing as the "baby boom" generation approaches menopause. Currently, over 30 million woman are postmenopausal, and the average life expectancy after menopause is 30 years.[1] Despite the well-recognized benefits of HRT with regards to heart disease and osteoporosis, concern about the risk of cancer seems to prevent some physicians from prescribing HRT and many patients from using HRT.

In this chapter, we will discuss the importance of counseling women on the benefits and risks about HRT to promote informed-decision making and we will review HRT and cancer risks. After a brief overview of menopause, we will review

the literature with regards to HRT and risk of the following cancers: endometrial, breast, ovarian, cervical, and colon. A separate discussion will address the use of HRT in cancer survivors, such as women with a history of breast cancer.

*Importance of Informed-Decision Making*

In a survey of women's attitudes about HRT, twice as many women reported being worried about breast cancer as reported being worried about heart disease.[2] When asked what illness they feared most, three times as many feared breast cancer as feared heart disease. In general, women perceived their risk for heart disease to be low and their risk of breast cancer to be high. In another study, the majority of women (80-85%) did not know that estrogen may decrease the chance of a heart attack and may increase the risk of endometrial cancer.[3] The most common reasons for postmenopausal women not using HRT in this study were they had never considered the treatment (70%) and had not discussed the treatment with a physician (79%).[3]

Decision making of women regarding HRT has been studied to assess what factors affect these judgments. Rothert et al. studied women between the ages of 45 and 55 who were not taking HRT to determine what factors were important in their decision not to use HRT.[4] The women in this study reported that their physicians did not listen to them and they felt like they had inadequate information to make decisions about HRT. The investigators studied the following factors: hot flashes, risk of fractures from osteoporosis, risk of endometrial cancer, and treatment regimen. Several important factors were not assessed at that time, namely heart disease and breast cancer. These investigators found that women fell into three main groups, each of which represented a different approach to the decision to use HRT. The largest group of women placed the most emphasis on relief of hot flashes and agreed to receive the combination of estrogen and progestin. The decisions of women in the second smaller group considered all the factors, including the risk of fracture and endometrial cancer, and were willing to receive the combination regimen. The third group also considered all the factors but were not willing to receive the combination therapy, possibly because they were not interested in resuming menstrual periods. This study found that the majority of women gave a high priority to the short-term relief of symptoms and did not make their decisions based on the risks of long-term outcomes, such as the risk of fractures.

Counseling patients about the benefits and risks of HRT is a complex process made particularly difficult by the need for probabilistic thinking, with which many patients are neither familiar nor comfortable. Nevertheless, patients want to be and should be involved in the decision-making process. Patient involvement is particularly important when the decision involves an intervention in asymptomatic patients, i.e. used for long-term benefits.[5] Patients need to have the critical facts to make these decisions, but many physicians may not be aware of the risks and benefits of HRT. The core information necessary for patients to make informed

decisions about HRT include: an understanding of menopause, the benefits from taking HRT considering the patients individual risk profile, the risk of developing cancer as a result of HRT, the potential need for endometrial biopsy if irregular bleeding occurs, the different regimens that are available, the frequency of physician visits required, and the duration of therapy necessary for maximum benefit of HRT (Table 1).

For most American women, natural menopause (the gradual cessation of ovarian function) occurs between the ages of 48 and 55 with a median age of 51.[6] The definition of menopause is generally accepted as the last spontaneous menstrual period that occurs as a result of the loss of ovarian function. During the few years approaching the average age of menopause (45-51), the majority of women experience a period of gradual reduction of and irregularity in menses known as the perimenopause.[7] Women who undergo bilateral oophorectomy, experience surgical menopause which is typically sudden and with more pronounced menopausal symptoms.[6]

Although the benefits of HRT are well accepted among many clinicians [8-12], only a small percentage of menopausal women use HRT. In the United States, striking differences in patterns of HRT use have been reported.[13] U.S. population-based prevalence rates of HRT use among menopausal women range from 8% in Massachusetts [14] to over 30% in California.[15,16] Since the 1930's, physicians have known that estrogen therapy reduces menopausal symptoms. The 1960's saw a dramatic increase in the number of women using estrogen. The number of prescriptions for estrogen decreased from 1975 to 1980 because of reports of an association of unopposed estrogen and endometrial cancer, and than increased through the mid-1980's.[17] Despite the research findings in the late 1980's and the 1990's that estrogen reduces the risk of osteoporosis and heart disease, many women still are reluctant to take estrogen because of the fear of both endometrial and breast cancer.[3] As with any form of medication, the benefit of relief of symptoms must be weighed against the risks or side effects. If women are to make such decisions about HRT based on evidence rather than fear, they need a clear understanding of their individual risks and benefits.

*Who uses HRT?*

Sociodemographic, medical and historical factors observed to be determinants of HRT use are listed in Table 2.[2, 18-25] Surveys on attitudes and knowledge of women regarding HRT use suggest that women know more about the potential risks, such as breast cancer, than about the proven benefits, such as preventing osteoporosis and heart disease.[2-3,19] Consequently, they may give more weight to the potential cancer risks of HRT than the benefits.

**Table 1.** Brief Instructions for a Assisting Patient with Decision Making on Hormonal Replacement Therapy.

*Start with a discussion of the condition and symptoms.* Women need to understand if they are perimenopausal, recently menopausal or post-menopausal. Discuss the effects of ovarian failure, i.e. menopausal symptoms and long-term effects. Explain why HRT is different from oral contraceptives (lower doses of estrogen) and therefore not contraindicated in women with a history of thromboembolic disease or cigarette smokers.

*Emphasize the proven benefits and potential for improvement in quality of life.* Note the improvement in overall survival, primarily conferred through a reduction in cardiovascular disease. Also note the improvements in bone density and subsequent reduction in fractures from osteoporosis. Mention the results of a few studies that suggest HRT may reduce the risk of depression, Alzheimer's dementia, and colon cancer.

*Acknowledge potential risks.* Discuss early problems with estrogen therapy (e.g. hot flashes, etc.) and the increased risk of endometrial cancer. Discuss the benefits of the addition of a progestin, if she has a uterus, to virtually eliminate the increased risk of endometrial cancer. Point out the continuing concern regarding an association between HRT and an increased risk of breast cancer. Emphasize that over 50 studies to date have not been able to demonstrate a significant association, except possibly for women with a family history of breast cancer and women who have used HRT for a long time. Reassure the patient that short-term HRT, especially for the relief of menopausal symptoms, has been shown not to increase the risk of breast cancer in very large studies of women.

*Discuss possible side effects.* At this time also discuss some of the side effects of inconveniences of HRT. If she has had a hysterectomy, she will only need estrogen and can choose oral versus the patch. Estrogen can cause some breast tenderness. Some women will tolerate estradiol better than conjugated estrogens. Explain that you will work with her to find the best regimen for her. If she still has her uterus, she will require a progestin and can choose several different combination regimens (see Table 2). The most bothersome side effect for most women is the return of menstrual periods and/or withdrawal bleeding. Progestin can cause some weight gain, fluid retention and mood swings, similar to Premenstrual syndrome. Many women tolerate continuous progestin (at a lower dose) better than cyclic progestin.

*Explain the necessity for additional monitoring.* Describe why before initiating HRT a mammogram is necessary. Patients need to understand that withdrawal bleeding may occur the first 6 months and that bleeding that occurs after this initial time may require endometrial surveillance with either ultrasound and/or biopsy.

*End with a discussion on compliance.* Acknowledge that studies have shown that many women who are given a prescription for HRT, never get it filled. Some women may be given prescriptions for HRT and not understand that they are menopausal. Offer written materials for her to read and suggest that she call you if she has further questions. Finally, women need to understand that although menopause symptoms last approximately 3 years, to maximize the benefits of HRT, long-term therapy (20-30 years) is warranted.

**Table 2.** Factors determinate of HRT use.

| *Women who use HRT are:* |
|---|
| thinner |
| more educated |
| middle to upper-middle income level |
| more likely to exercise |
| more likely to consume alcohol |
| more likely to have had surgical menopause |
| less likely to have a family history of breast cancer |
| in more frequent contact with physicians |

Understanding these determinants of HRT use (both "real" cancer risks and women's perceptions of cancer risks) is necessary for developing educational interventions that improve a woman's understanding of menopause and the risks and benefits of HRT use (see Table 3). Women opt to use HRT to alleviate menopausal symptoms, reduce their risks for heart disease and/or osteoporosis, or as part of a treatment plan for recently-diagnosed heart disease. Alternatively, women may choose not to use HRT due to cost, physician advice, unwanted side effects, withdrawal bleeding, inconvenience, and fear of the risks, especially the risk of breast cancer.[3]

**Table 3.** Common reasons women do or do not take HRT.

| *Do* | *Do Not* |
|---|---|
| Alleviate menopausal symptoms | Fear of breast cancer |
| Reduce risk of heart disease | Don't want to have periods |
| Prevent osteoporosis | Breast tenderness |
| Relieve genitourinary symptoms | Weight gain |
| | Withdrawal bleeding |

## Cancer Risks associated with HRT

*Endometrial Cancer*

Epidemiologic studies have suggested that there is an increased risk of endometrial cancer in postmenopausal women taking unopposed estrogen.[26-28] Unopposed estrogen can be defined as the use of estrogen for hormonal replacement without the addition of a progesterone. Endometrial hyperplasia, considered a preneoplastic

lesion, has been noted to develop in women treated with unopposed estrogens, and to regress after estrogen treatment is discontinued.[27] In the 1960's and early 1970's an increased incidence of endometrial cancer was observed to parallel an increase in the number of estrogen prescriptions.[29] Since 1970, at least 37 observational studies have examined the association between unopposed estrogen and endometrial cancer.[28] Using meta-analytic techniques to pool relative risk estimates from these studies, Grady et al. reported a summary relative risk of 2.3 (95% Confidence Intervals (CI) 2.1-2.5) comparing the risk of endometrial cancer in women who took unopposed estrogen at any time with those who never took estrogen.[28] However, the risk of endometrial cancer varied with the dose and duration of unopposed estrogen used (Table 4).

**Table 4.** Unopposed Estrogen Therapy and Endometrial Cancer Risk.[28]

| *Study Summary* | *Number of Studies* | *Meta Analysis Relative Risk Ratio* |
|---|---|---|
| Overall (ever users of unopposed estrogen) | 29 | 2.3 (2.1-2.5) |
| Dose (1.25 mg or more conjugated estrogen) | 9 | 5.8 (4.5-7.5) |
| Duration (more than 10 years estrogen use | 10 | 9.5 (7.4-12.3) |

The risk of endometrial cancer increases with the dose of unopposed estrogen. [30] Earlier studies probably overestimated the risk of endometrial cancer, as most of the patients in these studies were taking higher doses of estrogen (1.25-2.5mg) than doses commonly used today (0.625-1.25mg). In their meta-analysis, Grady et al. reported a summary relative risk of 5.8 (C.I. 4.5-7.5) comparing the risk of endometrial cancer in women who took 1.25 mg or a higher strength of conjugated estrogen at any time compared with those who never took estrogen.[28]

Several studies have demonstrated that the risk of endometrial cancer increases with increasing duration of unopposed estrogen use.[28,31] Using meta-analytic techniques, Grady et al. calculated a summary relative risk for endometrial cancer in women who used estrogen for 10 years or longer, as compared with those who never used estrogen, at 9.5 (CI 7.4-12.3).[28] Endometrial cancer is not very common; about 3% of postmenopausal women will develop endometrial cancer over the remainder of their lives.[11] If women took unopposed estrogen therapy

for more than 10 years, as many as 20% of postmenopausal women could develop endometrial cancer.[28]

Although endometrial cancer is a risk associated with unopposed estrogen therapy, women who develop endometrial cancer are usually diagnosed early (Stage 1) and have well differentiated neoplasms.[32] Fortunately, most endometrial cancers that occur in women taking estrogen can be treated effectively with hysterectomy. Studies have found an improved survival for women who developed endometrial cancer on estrogens compared to women who developed endometrial cancer off therapy.[28,33] This improved survival rate may be secondary to the increased surveillance of women on estrogens. It is also possible that the increased number of endometrial biopsies in women on HRT will detect previously unknown asymptomatic cancer. To evaluate this possibility, Horowitz performed an autopsy study to evaluate the number of patients with endometrial cancer unknown at the time of death.[34] Fifty-seven percent of all endometrial cancers were detected only at autopsy and were unknown at the time of death.[34] Another explanation for the possible increase in survival for women who develop endometrial cancer on HRT is the overall impact HRT has on survival (primarily through a reduction in cardiovascular mortality).[8] In contrast to this improved survival theory, other studies have shown an increased risk for late-stage, high-grade invasive tumors. [28,35] For example, results from a meta-analysis suggest an increased risk of death from endometnal cancer in ever-users of unopposed estrogen compared to never users with endometrial cancer (2.7, C.I. 0.9-8.0).[28]

To avoid the increased risk of endometrial cancer, women with a uterus should be treated with progestin. A number of studies (Table 5) have suggested that a progestin given for at least 10 days will virtually eliminate the risk of endometrial hyperplasia and cancer in women receiving estrogens.[28, 36-44] The rationale is that progesterone and synthetic progestin decrease the synthesis of estrogen receptors and thus suppress the proliferative effect of estrogens on the endometrium.

Since discovering that progestin is necessary to reduce the risk of endometrial cancer, investigators have explored different regimens for adding progestin to estrogen therapy (Table 6). The Postmenopausal Estrogen-Progestin Investigation (PEPI) study identified several different combination regimens that did not increase the incidence of endometrial hyperplasia or cancer.[44] Regimens studied in the PEPI trial (which was a randomized, double bind, placebo-controlled study) included placebo, unopposed 0.625mg conjugated estrogen, 0.625mg conjugated estrogen and 5mg progestin daily (continuous), and 0.625mg estrogen and 10mg progestin for 10 days per month (cyclic). Neither the cyclic nor continuous groups had a higher rate of hyperplasia than the placebo group. This study clearly showed an increased rate of endometrial hyperplasia in the unopposed estrogen group compared to the other treatments (34% versus 1%). No cancer was detected at three years in the cyclic or continuous groups, and one case of endometrial cancer was identified in the placebo and unopposed estrogen groups. The results of PEPI were similar to studies from the late 1970's and early 1980's. The importance of these

newer studies is they used lower doses of estrogen and evaluated several different estrogen/progesterone combination regimens.

**Table 5**. Summary of Endometrial Cancer Risk in studies using Combined Estrogen and Progestin*.

| *Primary Author* | *Type of Study* | *Relative Risk (95% CI)* |
|---|---|---|
| Nachtigall (1979) | Randomized Trial | ** |
| Hammond (1979) | Cohort | ** |
| Gambrell (1980) | Cohort | 0.2 (0.1-0.6) |
| Persson (1989) | Cohort | 0.9 (0.4-2.0) |
| Voigt (1991) | Case-Control | 1.6 (0.6-3.9) overall<br>0.9 (0.3-2.4) 10+ days progestin<br>2.0 (0.7-5.3) < 10 days progestin |
| Jick (1993) | Case-Control | 1.9 (0.9-3.8) |
| Brinton (1993) | Case-Control | 1.8 (0.6-4.9) |
| Woodruff (1994) | Randomized Trial | ** |
| PEPI (1995) | Randomized Trial | ** |
| Grady (1996) | Meta-analysis | 0.8 (0.6-1.2) overall<br>1.8 (1.1-3.1) case-control<br>0.4 (0.2-0.6) cohort |

* Modified from Grady, et al (1995).

**No endometrial cancer observed in the estrogen plus progestin group.

Endometrial cancer is not very common. A meta-analysis of studies which examined the association between unopposed estrogen and endometrial cancer found a summary relative risk of 2.3 (CI 2.1-2.5) comparing the risk of endometrial cancer in women who took unopposed estrogen at any time with those who never took estrogen.[28] Both increasing the dose and duration of unopposed estrogen therapy further increases the risk of endometrial cancer. Most women who develop

endometrial cancer on HRT can be treated effectively with a hysterectomy. To avoid the increased risk of endometrial cancer, women with a uterus should be treated with either cyclic or continuous progestin. Continuous therapy is an easier regimen to follow and potentially better tolerated by women who don't want to resume their menstrual periods.

**Table 6.** HRT Regimens Commonly Used in Clinical Practice

| *HRT* | *Administration* | *Advantages* | *Disadvantages* |
|---|---|---|---|
| Unopposed Estrogen | Continuous without cyclic progesterone withdrawal | Estrogen benefits<br><br>No withdrawal bleeding | Increases risk of endometrial cancer<br><br>Need for endometrial biopsy |
| Cyclic Estrogen and Progesterone | Estrogen 1-25 days, progestin 16-25 days | Reduces endometrial cancer risk | Withdrawal bleeding<br><br>5-6 days off can cause symptoms |
| Continuous Estrogen/ Cyclic Progesterone | Continuous estrogen/ progestin 10-14 days | Reduce estrogen withdrawal symptoms | Withdrawal bleeding |
| Continuous Estrogen and Progesterone | Continuous estrogen/continuous low dose progestin | Promotes anemorrhea<br><br>No withdrawal bleeding | Breakthrough bleeding<br><br>Need for endometrial biopsy |

*Breast Cancer*

As many as 40 observational studies of the association between the use of HRT and the risk of breast cancer have been published, yet no overall effect has been found.[45] Since some breast cancers are estrogen sensitive, it has been hypothesized that increased or prolonged exposure to estrogens would increase the incidence of breast cancer. Multiple studies have looked at the association of increased endogenous and erogenous estrogens and breast cancer.[46] Although the epidemiology of breast cancer suggests that endogenous estrogens such as

nulliparity, early menarche, late menopause, first child after age 30, not breast feeding, and obesity are important, a consistent effect of erogenous hormones such as HRT has not been clearly demonstrated.[47-48] As many as 6 meta-analyses have looked at HRT and risk of breast cancer and have confirmed the lack of an increased risk for breast cancer in the majority of women (Table 7).[11, 49-53]

**Table 7.** Summary of Breast Cancer Risk and HRT Use from 6 Meta-Analyses.

| *Primary Author* | *Number of Studies* | *Relative Risk (95% CI)* |
|---|---|---|
| Armstrong (1988) | 23 | 1.01(0.95-1.08) |
| Steinberg (1991) | 16 | 0.0 <5 years<br>1.3 (1.2-1.6) >15 years<br>3.4 (2.0-6.0) family history |
| Dupont and Page (1991) | 28 | 1.07 (1.0-1.1) |
| Sillero-Arenas (1992) | 37 | 1.06 (1.0-1.12) overall<br>1.23 (1.07-1.42) >12 years |
| Grady (1992) | 39 | 1.01 (0.97-1.05)<br>1.25 (1.04-1.51) >8 years |
| Colditz (1993) | 31 | 1.02 (0.93-1.12) |

There is no clear evidence of an association between the dose of estrogen and breast cancer risk. Dupont analyzed data from studies using conjugated estrogen 0.625mg dose and did not find an increased risk of cancer.[51] However, in some studies a dosage of 1.25mg increased the risk of breast cancer (RR=1.08).[51] When all studies using 1.25mg estrogen were compared, there was no increase in the risk of breast cancer. In a randomized controlled trial of 2.5mg estrogen with cyclic progestin 10mg for 7 days Nachtigall and colleagues report that no cases of breast cancer were found in the women taking HRT compared to 4.8% of women who developed breast cancer in the placebo group.[36] In 22 years of follow-up, 11.5% of the placebo group and none of the HRT group had developed breast cancer.[54] Nevertheless, the lowest dose of estrogen should be used to minimize side effects and any potential risk of breast cancer.

Most studies have not found an association between duration of therapy and breast cancer risk. A study by Newcomb et al., the largest case-control study to

date, did not find long-term HRT use to be associated with an increased risk of breast cancer.[55] Controversy, however, remains regarding breast cancer incidence in women who use HRT for extended periods (greater than 10 years). Three recent studies found no evidence of an increased risk of breast cancer in women who had taken HRT for 15-20 years or longer.[55-57] However, the fourth study from the Nurse's Health Cohort found a 30% increase in risk of breast cancer that was limited to current users who reported having taken HRT for more than 10 years; no associations were observed in long-term, past users.[58] The risk in this study increased with increasing age (over age 55) and duration of use (longer than 5 years). Although, after 2 years of not using estrogen, the increased risk of breast cancer disappeared. Despite ongoing controversy regarding long-term HRT use and an increased risk of breast cancer, studies consistently find no excess risk associated with relatively short-term (less than 5 years) HRT use.

Some studies have shown an improved prognosis of breast cancer in HRT users. [47] These studies have shown that women on HRT have earlier detection of their cancers. This has been proposed to reflect both patient awareness and increased surveillance by their physicians. Also HRT users are more likely to have positive estrogen and progesterone receptors in their breast cancers, which seems to be an additional factor that improves their prognosis. A recent British study [59] prospectively studied 433 postmenopausal women with invasive breast cancer detected by mammographic screening; 108 were HRT users. HRT users were significantly more likely to have well-differentiated, grade I tumors (45% versus 20%). Tumor size, steroid receptor status, and positive axillary nodes were similar in the HRT user and non-user groups, as were recurrence rates over a median follow-up of 45 months. Because HRT users had a higher prevalence of grade I tumors, the investigators predict a higher likelihood of survival. Since tumor size and axillary node status were similar, the authors have argued against the differences resulting from different screening practices for the two groups. Yet, a recent epidemiologic study identified an increased risk for *in situ* breast cancer associated with HRT use (odds ratio 1.6 (C.I. 1.0-2.58).[60] Further research is needed in this area since previous studies have not accounted for the differences between HRT users and nonusers that may affect mortality.

With the addition of progestin to HRT in order to reduce or eliminate the risk of endometnal cancer, researchers have been concerned about the potential increase in risk of breast cancer. The effect of progestin on breast cells is not the same as their effect on endometrial cells. Increasing levels of progesterone in the luteal phase produce further increases in mitotic activity in breast cells (while decreasing mitotic activity in endometrial cells).[61] Earlier studies suggested an increase in risk of breast cancer in women using estrogen and progesterone replacement therapy [62,63], while other studies suggested a decrease in the risk of breast cancer.[36, 54, 64] Recent studies do not suggest a significant increase in the risk of breast cancer with the current combination regimens (Table 8).[55-58] Further research is needed to determine if the different combination regimens, i.e. continuous versus cyclic progestin, have different effects on breast tissue.[7]

**Table 8.** Breast cancer risk in recent studies of HRT that include estrogen and progestin.

| *Primary Author* | *Type of Study* | *Relative Risk (95% CI)* |
|---|---|---|
| Schaierier (1994) | Cohort | 1.2 (1.0-1.6) ever used |
| Colditz (1995) | Cohort | 0.9 (0.77-1.05) ever used<br>1.32 (1.14-1.54) current use<br>1.41 (1.15-1.74) current use, estrogen/progestin<br>1.46 (1.2-1.76) >10 years |
| Stanford (1995) | Cohort | 0.9 (0.7-1.3) ever used<br>0.4 (0.2-1.0) >8 years |
| Newcomb (1995) | Case-Control | 1.05 (0.9-1.2) ever used<br>1.11 (0.87-1.43) >15 years |

Consistent results of multiple studies indicate no increased risk of breast cancer with use of HRT. The American Cancer Society estimates that 182,000 new cases of breast cancer would be diagnosed during 1996 and that 46,000 women would die of this malignant neoplasm in 1996.[45] The mortality from breast cancer in the United States is 22.4/100,000.[46] The most recent studies do not suggest a significant increase in the risk of breast cancer with the current combination regimens.[65] Studies consistently find no excess risk associated with relatively short-term (less than 5 years) HRT use.[66] Exceptions to this include long-term HRT users and individuals already at an increased risk because of a family history of breast cancer.

*Ovarian Cancer*

Certain risk factors are shared by both ovarian and endometrial cancer (e.g., nulliparity) and when endometrial cancer was found to be associated with unopposed estrogen therapy, it was proposed that there might be a similar increase in the risk of ovarian cancer. Others have argued that estrogen therapy might reduce the risk of ovarian cancer, because oral contraceptives are known to reduce the risk.[67] Epidemiologic studies have not found an association between HRT and ovarian cancer. The Surveillance, Epidemiology and End Results (SEER) program performed between 1975 and 1977, did not identify an increase in the overall incidence of ovarian cancer, but did note a rise in the number of

endometrioid ovarian tumors.[68] Since these endometriold ovarian carcinomas are histologically similar to endometrial carcinomas, further studies were conducted to examine this potential association, and no significant increase in any type of ovarian cancer could be found associated with HRT use.[69]

*Cervical Cancer*

There are no epidemiologic studies to suggest an association between cervical cancer and HRT use.[67] HRT has not been found to have any effect on the incidence or recurrence of cervical cancer, or on the natural history of carcinoma in-situ.

*Colon Cancer*

Colon cancer is the only cancer that occurs with almost equal frequency in men and women; yet, certain characteristics of colon cancer epidemiology suggest that risk may be influenced by endocrine factors.[70-72] Recognition of the association between reproduction and hormonal status and colon cancer began with the observation of Fraumeni, et al. in 1969 that nuns experience an excess, not only of female cancers (breast, ovary, and endometrium) but also of colon cancer.[73,74] In the 1970's, there was a modest decrease in the incidence of colon cancer among women compared with men, at the time that oral contraceptives and HRT had become common. During the last 30 years, mortality from colon cancer has declined 21% for women, while increasing 16% for men.[75]

There is significant controversy in the literature about HRT as a risk for colon cancer. Six [76-81] of 11 [82-86] recent studies have found that HRT use is associated with a lower risk of colon cancer (Table 8). The most recent study, by Newcomb et al., is the largest case-control study published to date.[81] Overall, they found HRT use was associated with a significant reduction (about 30% for ever use and 46% for recent use) in colon cancer incidence. This inverse association with risk for colon cancer was observed among users of both estrogen only and estrogen and progestin combination therapy, and was maintained for at least 10 years after stopping HRT use.

## HRT use in Cancer Survivors

*Endometrial Cancer*

A contraindication to HRT is an estrogen-dependent neoplasia; however, Stage 1 endometrial cancer is not a contraindication.[87] Creasman et al. found those patients with Stage I endometrial cancer treated with estrogen survived longer than those who were not treated with estrogen. Lee et al treated patients with endometrial cancer (low-grade lesions, less than 50% local invasion, and without nodal metastasis) with estrogen. In 5-year follow-up, no recurrence of endometrial

**Table 8.** Selected Studies Suggesting that there Might be a Decrease in Colon Cancer Risk with HRT Use.

| *Primary Author* | *Type of Study* | *Relative Risk (95% CI)* |
|---|---|---|
| Fumer (1989) | Case-Control | 0.5 (0.27-0.9) ever used |
| Chute (1991) | Cohort | 0.7 (0.4-1.1) |
| Gerhardsson de Verdier (1992) | Case-Control | 0.6 (0.4-1.1) |
| Jacobs (1994) | Case-Control | 0.6 (0.35-1.01) ever used<br>0.47 (0.24-0.91) >5 years |
| Bostick (1994) | Cohort | 0.82 (0.5-1.32) current use |
| Newcomb (1995) | Case-Control | 0.73 (0.56-0.94) ever used<br>0.54 (0.36-0.81) current use |

cancer was identified in the treatment group and a higher mortality was observed in the control group from cardiovascular disease.[88] Guidelines for the use of estrogen therapy in endometrial cancer survivors have been proposed: 1) estrogen receptor (E) and progesterone receptor (PR) status should be determined at the time of surgical staging; 2) patients who are determined to be at low risk for recurrence may begin estrogen therapy; 3) patients who are determined to be at high risk for recurrence, but are E negative may begin estrogen therapy; and 4) patients who are determined to be at high risk for recurrence and are E positive are to be monitored for a 3 to 5 year disease-free interval prior to initiating estrogen therapy.[89]

*Breast Cancer*

Many women are surviving breast cancer and a large proportion of women who are pre-menopausal when breast cancer is diagnosed, develop chemotherapy-induced menopause.[90] Although having a history of breast cancer is a relative contraindication to HRT, some physicians prescribe HRT for survivors of breast cancer, especially those with severe menopausal symptoms.[91] A few studies have looked at the impact of HRT in breast cancer survivors.[92-94] The most recent study from Australia found no deaths and significantly fewer recurrences in patients who were given continuous estrogen-progesterone compared to controls (despite the high doses of progestin, 10-20 times higher than used in U.S.).[94] While the

definitive prospective studies to show that HRT is safe in survivors of breast cancer are still needed, the risks and benefits of HRT should be discussed.

Many women who have had breast cancer are aware of the benefits of HRT (especially protection against cardiovascular disease) and are asking their physicians (often their oncologist) to help them make a decision about HRT.[45] Tamoxifen may be a safer alternative to conventional HRT in women who have had breast cancer. It is both an estrogen antagonist and agonist. When tamoxifen is given in the presence of estrogen (premenopausal), it antagonizes estrogen (causes hot flushes). In the absence of estrogen (postmenopausal) it behaves as an estrogen (increases bone density and protects against cardiovascular disease). It is always an anti-estrogen on the breast. A Scottish study of breast cancer patients showed that patients who received tamoxifen as adjuvant therapy were less likely to experience a fatal myocardial infarction (hazard ratio 0.37 (C.I. 0.18-0.77).[95] In a study by Love et al., breast cancer patients were given 20mg of tamoxifen or placebo, those on tamoxifen experienced a slight increase in bone density.[96] Another study by Love found that tamoxifen lowers LDL cholesterol with little effect on HDL.[97] Thus, tamoxifen is thought to act like estrogen on the liver. Because tamoxifen acts like an estrogen on the uterus, there is growing concern about the need to add a progesterone to prevent endometrial cancer. Agents, such as progestin and Megace, have been considered but they also have side effects. The studies available to date suggest that tamoxifen protects against cardiovascular disease and osteoporosis with a similar impact to HRT. Unfortunately, tamoxifen does not improve hot flashes, and in some cases makes them worse. Therapies, such as clonidine, can be considered for severe hot flushes, when HRT is contraindicated.

## Conclusion

HRT has been shown to reduce all-cause mortality (primarily through a reduction in cardiovascular mortality).[8] Although, overall the benefits appear to outweigh the risks, each woman together with her physician must develop her own risk profile before a decision is made about HRT. Other benefits besides the cardiovascular and osteoporosis benefits should be considered, such as, the symptomatic relief of hot flashes, vaginal dryness, and insomnia, and the emerging evidence that HRT may have a beneficial effect on cognitive functioning (delaying the onset of Alzheimers), as well as possibly reducing the risk of colon cancer.

Although controversy exists with regards to the benefits and risks of HRT, the Women's Health Initiative sponsored by NIH, has been designed to test many of these effects. The primary outcomes to be studied are cardiovascular disease, breast cancer, colorectal cancer, and osteoporotic fractures. The interventions include a trial of HRT, a trial of a lowfat diet to prevent breast and colon cancer, and a trial of calcium and Vitamin D to prevent osteoporotic fractures. The answers to the primary design questions will be available by the year 2007.[98] Questions that still need to be addressed include 1) the effects of HRT from randomized trials that eliminate the problems of selection bias, 2) effects of HRT in specific subgroups,

i.e. women with known family history of breast cancer or the BRCAL or BRCA2 cancer genes, 3) more information about the effects of HRT using continuous versus cyclic progestin therapy or other progesterone compounds, and 4) and more information from long-term studies.

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# BREAST CANCER PRACTICE PATTERNS AT VA HOSPITALS: IMPLICATIONS FOR FUTURE RESEARCH

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## Introduction

Cancer incidence among women veterans has been estimated to be twice that of the general population.[1] Current estimates that one out of nine American women will develop breast cancer in their lifetime [2], translates into an estimated 133,000 veterans who will develop breast cancer. Currently there are over 1.2 million women veterans in the United States and approximately 10% of active duty military officers and enlisted personnel are women.[1,3] One out of every ten women veterans have used inpatient services at a VA hospital since leaving the service.[3] In particular, the use of breast cancer screening and treatment services by female veterans has been substantial and is increasing steadily. In Fiscal Year (FY) 1994, over 1,300 women had a breast cancer-related admission to a VA hospital.[4] With the current breast cancer incidence estimates, the aging of the women veteran population and the increasing demand for women's health care services at VA

hospitals -- and for breast cancer care in particular -- practice patterns at VA hospitals can have dramatic impacts on the health of women veterans.

The VA has always provided medical treatment to women but according to past GAO reports, not always with the appropriate sensitivity, physical accommodations or equipment necessary to provide comprehensive care.[5] These findings raise concern about the adequacy of the VA health care system to meet the needs of women veterans, especially with regard to breast cancer screening and treatment. As of 1992, only 90 of the 172 VA hospitals had a women's health clinic and 25 had on-site mammography units.[5-6] Improvements have been seen over the last three years such that there was an increase of 15% in the number of mammograms performed under VA auspices from 20,963 in 1993 to 24,117 in 1994.[7] As a result of Public Law 102-585, eight Women Veterans Comprehensive Health Centers (Boston, Chicago, Durham, Minneapolis, San Francisco, Sepulveda/West Los Angeles, and Tampa), were established in FY93-94 to develop new and enhanced programs focusing on the unique health care needs of women veterans. The Women Veterans Health Program Act of 1992 authorized new and expanded services for women veterans, including counseling for sexual trauma on a priority basis; and specific health services for women, such as Pap smears, mammography, and general reproductive health care. In FY93, $7.5 million, and in FY94, $12 million were appropriated for these more comprehensive services for women veterans in the VA health care system. However, most VAs still provide so few services to women that the quality of care, in particular for breast cancer screening and treatment, could be called into question, especially at those facilities that provide a low volume of services. While the oncology community has established consensus guidelines on breast cancer screening [8] and treatment [9], whether practice patterns at VA hospitals conform to these standards is unknown.

This chapter explores practice patterns for women seeking breast cancer care in the VA health care system from 1991 through 1994. Data are derived from a larger study of breast cancer prevention and treatment issues in the VA.[10] Several issues are raised for further evaluation and issues for future research in women's health care at VA hospitals are suggested.

## Practice Variations in Breast Cancer Treatment

Treatment for breast cancer is vital to ensure full recovery from the cancer, to prevent recurrence of the cancer in the opposite breast, to restore physical functioning to the affected side, and to facilitate emotional recovery.[11,12] Appropriate treatment is determined by clinical (or pathological) staging of the disease and may include observation, surgery and adjuvant therapy either single mode or multi-modal therapy.[9] During the 1990's, patients are being treated at earlier stages of the disease as compared to the 80's.[13] Surgical treatment for conservation of the breast is being used more frequently but modified radical

mastectomy is the most common primary surgery for treatment of breast cancer. [13]

Previous research has demonstrated practice variations for breast cancer. Differences in surgical treatment have been reported within local communities in the U.S.[ 14] , across the U.S. [15, 16], and abroad.[17,18,19] Patient, provider and facility characteristics have been shown to affect surgical practice patterns. For example, Hynes [16] found that older women with breast cancer in local communities were less likely to have a two-step surgical procedure. Most recently, in a study of hospitals treating elderly breast cancer patients from 1986 to 1990, Nattinger and colleagues [15] found that facilities with higher patient volumes were more likely to use breast conserving surgery.

Differences in adjuvant therapy use have also been shown to vary with patient age, with several studies finding that older women are less likely to receive adjuvant therapy.[16,20-24] Physicians who treat more breast cancer patients have been found to make clinical judgements consistent with NIH Consensus Conferences on breast cancer [25], although consensus guidelines do not seem to have a consistent impact on physicians practice styles.[26] Breast cancer patients treated by physicians involved in clinical trials research have also been shown to be more likely to receive adjuvant therapy compared to those treated by physicians not involved in research.[21,25]

## Hypothesis

We expected that breast cancer practice patterns at VA hospitals would be comparable to that found in community studies for diagnostic patterns, such as use of breast biopsy; and, for treatment patterns, such as use of surgery and rates of adjuvant therapy use. We also anticipated that, with the new programs and expanded services made available to women veterans with the implementation of Public Law (P. L.) 102-585, the Women Veterans' Health Program Act of 1992, breast cancer practice patterns would improve. In particular, we expected that women would tend to be diagnosed at an earlier stage after implementation of the Act compared to before.

## Methods

*Sample of VAMCs*

We selected a convenience sample of eight VAMCs from which to solicit medical records of breast cancer patients hospitalized in 1991-94. These sites were selected based on the number of breast cancer cases, the capacity of the local Decentralized Hospital Computer Program (DHCP) Health Summary, and the status of the implementation of the DVA Patient Data Exchange (PDX) Software system, an electronic data capture system that interfaces with the local DHCP Health Summary

(which just became available Summer, 1994). Of the eight sites originally solicited to participate in our field test of this electronic data capture of medical records, six sites participated. These VAMC sites included Boston, Brooklyn, Durham, Hines, Phoenix, and Tampa.

*VAMC Cancer Criteria and Identification*

For each participating VAMC we identified cases from the VA Patient Treatment File (PTF) that had any of the following breast cancer related discharge diagnoses: ICD-9-CM 174, 233.0, 217, 238.3, 239.3. The names, SSN, admission and discharge dates were then submitted to the VAMC via PDX software.

*VAMC Record Co-Detection and Abstractions*

We developed a unique approach to obtaining medical record data electronically using the VA's Decentralized Hospital Computer Program (DHCP). We first developed a medical record abstract form for abstracting selected information from patient's medical records and then designed a customized electronic patient health summary for extracting comparable information from the patient's electronic record. We requested copies of the patient's Breast Cancer Health Summary be sent to us electronically via EMAIL or as hardcopy. These electronically produced records were then abstracted using the record abstract form that we developed. Two study assistants were trained by two clinicians in the study team (LB and DH, a physician and nurse, respectively), in the use of the abstract forms for the two record types. All abstracts re-reviews were performed by these clinicians.

To validate this approach for electronic data capture and abstraction, we also obtained a 20% sample of medical charts and abstracted these and then compared our electronic data abstracts with the abstracts of the medical record abstracts. Validation of this approach is reported elsewhere.[10]

*Analysis of Specific Practice Patterns Among Women Treated at VAMCs*

For cases that were determined to be new onset breast cancer cases we conducted descriptive analyses to assess trends in breast cancer practice patterns. Specific practice patterns studied included diagnostic patterns, such as whether mammography was used, whether breast biopsy was performed, whether tumor staging characteristics criteria, (i.e., size, nodal status and metastasis) were used; and treatment patterns including whether surgery was performed and whether adjuvant radiation, hormone or chemotherapy were used. In particular we were interested in examining trends by age group and before and after the implementation of the Women's Health Act. Although Congress passed the Women's Health Act in 1992, it was not until October of 1993 (FY94) that most facilities received their funding and initiated improvements in women's health care. So, for comparisons before and after the implementation of the Women's Health

Act, we compared practice patterns in FY91-93 with practice patterns in FY94 for all analyses.

## Results

*Record Retrieval Rate*

Figure 1 shows the break out of the requested records and their level of completeness for purposes of abstracting information about follow-up. Records for 167 unique patients were reviewed for this study. However of these cases, 72 were excluded due to lack of clinical components in the record (38 cases), diagnoses of benign breast disease (24 cases), and previous history of breast cancer only (10 cases). Thus, 95 breast cancer cases were available for analyses: 67 cases were diagnosed at VA facilities.

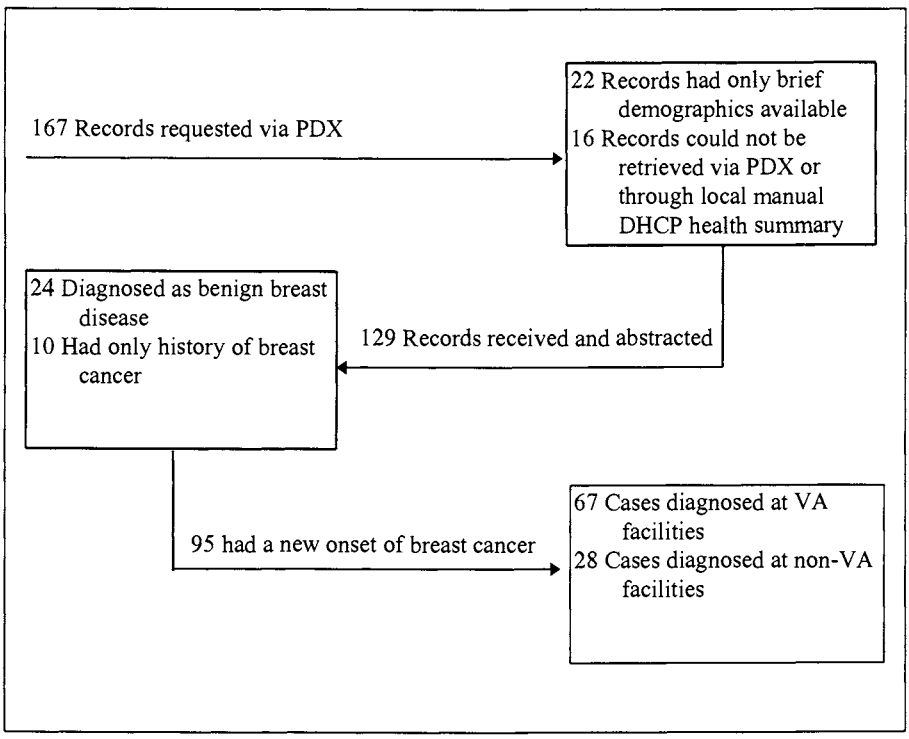


**Figure 1.** Retrieval Rate of Requested Records and Reasons for Exclusion.

*Summary of VAMC Breast Cancer Practice Patterns*

Table 1 summarizes the practice patterns studied for the 95/167 cases determined to have new breast cancer diagnoses. Ages ranged from 30-90 years, with a mean age of 65 years. 80 % were age 50 or over. 36 % of cases were service connected and 23 % were married at the time of their admission. 36 % of patients had a documented mammogram before any treatment was administered, and 70% had documentation of a breast biopsy. 76% of patients had some type of surgery for treatment of their cancer. 23 % had documented radiation therapy, 23 % had documented chemotherapy, and 32% had documented hormone therapy. Tumor size information was documented on only 54/95 (57%) cases, and of these 50% had tumors that were 2.0 cm or larger. Lymph node status was documented on only 45/95 (47 %), and of these 32 % had positive lymph nodes.

**Table 1.** Selected Breast Cancer Practice Patterns for Women Treated at 6 VAMCS, 1991-1994.

| *Selected Practice Pattern* | *Frequency (%) (n= 95)* |
|---|---|
| Breast biopsy performed | 67 (70) |
| Size of tumor noted | 54 (57) |
| Lymph nodes examined | 45 (47) |
| ER assay performed | 23 (24) |
| PR assay performed | 21 (22) |
| Any surgery | 72 (76) |
| Any mastectomy | 57 (60) |
| Any chemotherapy | 22 (23) |
| Any hormone therapy | 30 (32) |
| Any radiation therapy | 22 (23) |

Information for specific tests, procedures, and initiation of adjuvant therapy had a large degree of missing data. For example, for whether the patient had any cancer directed surgery, data were missing for 23 % of the cases; estrogen receptor status was missing on over 75 % of the cases; information on adjuvant therapy was missing on 67-76% of the cases. In some instances we were able to assume that 'no data' was equivalent to not having the procedure done.

*Comparison Before and After the Women's Health Act of 1992*

In order to monitor trends in health care for women veterans since the implementation of the Women's Health Act in 1992, we compared demographics

and health care utilization in cases diagnosed in VA facilities in FY91-93 to FY94. As shown in Table 2: 67 breast cancer cases were diagnosed in VA facilities overall. Although the numbers are small in this pilot study, trends were noted towards improved access to care for non-service connected women veterans with breast cancer (70 % versus 47 %, p = 0. 08) since the implementation of the Women's Health Act. We also observed that women were being diagnosed earlier in their disease with more women diagnosed as Stage I and more women undergoing breast conserving surgery. There was also a trend toward decreased use of adjuvant therapy.

**Table 2.** Frequency of Practice Patterns Before and After the Women's Health Act of 1992 (Implementation in Fiscal Year 1994) for Breast Cancer Patients Diagnosed at VAMCs.

| *Characteristic* | *Fiscal Year* | | *P value* |
|---|---|---|---|
| | FY 91-93 (n=47) | FY 94 (n=20) | |
| Age >65 | 62% | 55% | 0.60 |
| Non-Service | | | |
| Connected/No | 47% | 70% | 0.08 |
| Pension | 25% | 20% | 0.60 |
| Married | 74% | 89% | 0.20 |
| Mammogram Ever | 15% | 20% | 0.60 |
| Diagnosed Stage I | 18% | 39% | 0.10 |
| Breast Conserving Surgery | 23% | 15% | 0.40 |
| Radiation Therapy | 32% | 25% | 0.60 |
| Hormone Therapy | 23% | 10% | 0.20 |
| Chemotherapy | | | |

## Discussion

We found that hormone receptor status was under-utilized in VA hospitals. This finding is consistent with patterns found in non-VA hospitals. Reported rates of hormone receptor status assessment in medical record review studies range from 46% [27] to 61 % [28], thus the 23 % rate we observed is low, by comparison. It is possible that documentation in VA records, the primary source of data in our study, is not as complete as that in non-VA settings. Since women veterans tend to be referred outside of the VA for some portion of their care, it is likely that information from services provided outside the VA are poorly documented in the VA record. However, we focused our study on women whose VA hospital admission was for the primary treatment of their breast cancer. Availability of

diagnostic information in the VA record is essential for the treating clinician, in this case, the VA physician, and efforts need to be made to improve information transfer between clinicians.

Given the limitations of medical record documentation, the rate for hormone receptor status assessment is low in the VA. This low rate, while not surprising, is still unsettling because exact treatment planning is not possible without hormone receptor assessment, according to the 1992 International Conference on Adjuvant Therapy of Primary Breast Cancer recommendations.[9] There seems to be some resistance on the part of clinicians to assess hormone receptor status. While efforts to improve clinicians' assessment of hormone receptor status in breast cancer patients are needed, the question remains whether such lack of adherence ultimately affects patient outcomes, and should be evaluated in both VA and non-VA settings.

We also found low rates for adjuvant therapy use. Low rates of adjuvant therapy (radiation, hormone and chemotherapy) use may be because women were being diagnosed earlier, but also may be a truncation effect since the later cases may not have been observed long enough to detect an occurrence of such treatment. An additional concern is the extent to which there may also have been some left censoring of data. In other words, we may have missed some cases for whom information in the VA medical record was not available to determine that the case had been diagnosed at a VAMC. A prospective study design could alleviate both of these problems by supplementing medical record data with additional patient questionnaire data and follow-up with VA and non-VA providers.

Finally, we observed trends toward improved access to care since the implementation of the Women's Health Act. Studying a larger number of patients over a longer time period would be desirable to validate our findings and to determine whether some of non significant findings were constrained by sample size alone.

## Issues for Future Research

Management of breast cancer at VA hospitals is especially challenging because often patients receive care from multiple providers. Women veterans may seek care at VA facilities during a treatment phase or in follow-up, but breast screening and some treatment may be provided elsewhere. Information from the continuum of care, such as results of mammography, staging of cancer, or specific information that may determine treatment, are often not documented in the VA medical record. Researchers must be cognizant of the episodic nature of health care for women treated at VA facilities and practice pattern studies should be designed to capture this process. VA practice pattern studies should be clinically relevant, for example, by identifying specific strengths and weaknesses in the care process. In this way clinicians and managers can build on identified successes and modify identified deficiencies.

Future studies of practice patterns of women treated at VA facilities must be aware of the referral system used, especially for female-specific services that may not be widely available at VAMCS. Even facilities that provide more comprehensive services for women veterans subcontract some services to affiliated hospitals, especially for procedures requiring the services of a subspecialist, such as breast biopsies and gynecologic surgeries. Utilization of subcontracted services are not well documented in the VAMC records in spite of the fact that follow-up care may be provided at the VAMC. Lacking information for services provided offsite from the VAMC for a population of patients who by necessity must receive some of their care off-site is particularly problematic for timely clinical decision making. A unique aspect of the VA is its ability to implement new programs on a large scale through its large network of hospitals and clinics and linked information systems. Implementation and research efforts that can demonstrate the most effective approach to facilitate information transfer and to promote .fully informed clinical decision-making have the most potential to improve practice patterns across VA hospitals.

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# HEALTH SERVICES RESEARCH IN HEAD AND NECK CANCER

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## Introduction

Scientists have studied the benefits of medical interventions for centuries. With the rapid evolution and growth of social medicine in the post-World War II era, research methods developed by clinical epidemiologists, demographers, economists, management theorists, psychologists, and statisticians joined traditional epidemiological research in studies of the medical care field. Utilizing these techniques and those that traditionally have been used by clinicians, a new field of research evolved which is frequently called "health services research". It is best viewed as a field not a discipline, and for the most part is population-based.[1]

The review presented here focused on recent literature (1991-1996) identified from Medline databases under the general heading of head and neck cancer with specific reference to the following key words: access, cost, decision analysis, epidemiology, psychosocial, quality of care/quality of life, policy, and workforce. Directed searches based on the bibliographies of certain papers were also performed. Over 1,500 articles were identified. After a review of citation titles, and if necessary abstracts, approximately 10% were selected for more detailed assessment, with 82 chosen ultimately for use in this chapter.

Head and neck cancer can be defined in many ways. Most commonly, however, the term applies to squamous cell cancers of the upper aerodigestive tract (i.e., oral

cavity, larynx, pharynx).[2] For purposes of this chapter, head and neck cancer was defined in this manner. Some of the articles reviewed are not specific to head and neck cancer, but were included because an important theme or concept applicable to this group was emphasized.

This overview is conducted in an era of increasing attention to cost-effectiveness and the concomitant growth of managed care. These two factors serve as the backdrop for this chapter. The review is organized into seven major sections in order to group the relevant literature into more homogeneous categories. These sections are entitled epidemiology and risk factors; access to care; prevention and screening issues; patient needs; outcomes of care; cost of care; and workforce issues.

## Epidemiology and Risk Factors

There were approximately 41,090 new cases of head and neck cancer (3. 0% of all cancer) diagnosed in the United States in 1996, with 12,150 deaths (2.2% of all cancer deaths). The disease is most common in older patients (age $\geq$50 years), and the age-adjusted incidence is highest among black males. Worldwide, more than a half million new cases are projected annually, with the disease posing a special burden in third-world countries.[2-4] Tobacco (cigarettes, pipes/cigars, smokeless tobacco) and alcohol consumption are the most important risk factors, and their risk may be multiplicative for certain sites. The central role of these two risk factors explains the high rate of second primary tumors (approximately 4%/year) and medical comorbidities found in these patients. These two factors obviously complicate management, impact on outcome, and affect the consumption of health services. Other commonly mentioned associations include diet (e.g., vitamin A and its analogues may be protective), mouthwash use (related to alcohol content), viral infection (e.g., human papilloma virus for squamous cell carcinoma, Epstein-Barr virus for nasopharynx cancer), and genetic susceptibility.[2,4]

Studies using varying sample sizes (n=47 to 4,506) have been conducted to elucidate the impact of specific prognostic and risk factors on outcome. The impact of site and stage of disease on survival is widely appreciated.[5] After controlling for age, gender, T stage, N stage, clinical stage, type of treatment, lymph node and margin status, Barra et al. found that transfused patients had a two-fold lower survival rate compared to non-transfused patients.[6] Brownian et al. identified cigarette smoking during radiation therapy as impacting negatively on the efficacy of treatment.[7] Pelczar et al. reported that the strongest predictors of medical complications following surgery were poor functional capacity and alcohol abuse.[8] They further noted that the strongest predictors of wound infection were an elevated preoperative platelet count and prolonged surgery; wound infection was the strongest correlate of prolonged hospital stays. Hussain et al. assessed the risk factors for infection in patients with head and neck cancer undergoing multimodality therapy. The presence of a foreign body (e.g., intravenous cannulae,

gastrostomy tube), race (black), performance status (lower), alcoholism, and malnutrition were all significant on univariate analysis. Presence of a foreign body and performance status remained significant on logistic regression.[9]

## Access to Care

Access to care is a major societal concern despite the new emphasis on cost-consciousness. From a patient's perspective, the major barriers to access are the absence of health insurance coverage, inadequate coverage, and incomes below the poverty level.[10-13] These issues are especially problematic for the poor, elderly, and minorities, groups that have a higher risk of developing head and neck cancer. Reimbursement policies also affect disease prevention and clinical research.[14] Blacks, who have the highest cancer incidences and mortality rates, have the greatest access problems.[15]

Beliefs and attitudes of professionals providing care is a further problem.[16] Reporting on testimony by professionals at a series of nationwide hearings in 1989 sponsored by the American Cancer Society, Underwood noted the following: the disadvantaged, who are often stereotyped, are a population disliked and disowned by much of society; their survival is often contingent on rationing the basic necessities of life; the culture and experiences they share are not well understood; and they are often obliged to serve the profession as "teaching material" in exchange for health care. The obstacles encountered by professionals who tried to provide care included the beliefs and attitudes of their peers, processes and systems that discourage referrals, and limited access to resources.

## Prevention and Screening Issues

Many health policy experts believe that prevention is the best way to address cancer problems. Estimates suggest that at least 70% of cancers are preventable if certain high-risk behaviors are modified.[17] The development of effective strategies for the prevention of head and neck cancer requires a thorough understanding of potential risk factors for the disease as described previously. The known high incidence of second primary tumors in this population must also be considered.

An article prepared by staff from the National Cancer Institute outlines Prevention actions amenable to use by physicians as part of any cancer prevention program, including head and neck cancer.[17] Screening for oral cancer by physicians is especially important among the elderly, who are two to three times more likely to see their doctor than their dentist.[18] Prout et al. [19] developed a program for primary health care providers to incorporate head and neck cancer screening into the routine care of patients at risk for these cancers. This program entails an exam which provides the necessary data to complete an oral cancer screening form (encompassing questions on risk factors, symptoms, physical examination findings, and scheduling follow-up based on the information

provided), the establishment of criteria for identifying a "positive" screen, and lectures-slide presentations for different categories of medical personnel. Use of this program in one site resulted in a large increase in screening for these cancers (90% of at-risk patients) compared with baseline rates (3%). Of note, Talamini et al. found that among patients at high risk for head and neck cancer, female sex, the absence of symptoms, current smoking, and younger age were associated with lower compliance with a head and neck cancer detection program.[20]

Gritz et al. reported on a randomized controlled trial comparing a state of the art, provider-delivered smoking cessation intervention to usual care advice in newly diagnosed, head and neck cancer patients.[21] The intervention consisted of surgeon- or dentist-delivered advice to stop smoking, a contracted quit date, tailored written material, and booster advice sessions. At randomization, 88.2% of eligible subjects (n=186) were current smokers; at 12-month follow-up 61% (114/186) of the subjects completed the trial. Although the intervention itself was not a significant predictor of 12-month continuous abstinence (p=0.33), its coefficient had the expected positive sign. Multivariate analysis identified treatment (not radiation only), readiness to quit, younger age, nicotine dependence (>30 minutes to first cigarette), and race (non-white) as significant predictors for continuous abstinence.

Accumulating evidence suggests that retinoids are important in the prevention of epithelial carinogenesis. In a randomized study from MD Anderson Hospital [22], patients who were disease free after treatment of their primary head and neck cancer were randomized to 13-cisretinoic acid (13-cRA, 50-100 mg/m2 by mouth daily) or placebo for 12 months. There was no difference between the two treatment arms in the number or pattern of relapses, or overall survival, but there was a significantly decreased rate of second primary tumors on the 13-cRA arm. About 20% of patients in the 13-cRA group did not complete treatment because of toxic effects. Although chemopreventive agents are not routinely indicated in clinical management of patients with head and neck cancer, the investigation of vitamin A and its analogues as well as other potential chemopreventive agents represents an important and rapidly evolving area of cancer research.

## Patient Needs

Patients with head and neck cancer often need assistance with activities of daily living as a result of therapy or the natural history of disease. While the literature identified in this area is not specific to head and neck cancer patients, it is nonetheless instructive. Based on a longitudinal study of the home care needs and services used by 434 patients with cancer at initiation of chemotherapy or radiation therapy in Central Pennsylvania, Rhode Island, and New York City, Mor et al. [23] reported the following needs at follow-up (3 to 6 months after baseline): physical (personal) activities of daily living (16%), instrumental activities of daily living (45%), transportation (47%), and home health (11%). The acquisition of new needs

at follow-up was associated primarily with disease and treatment-related characteristics. For example, significant relative risk ratios for the main category of transportation need were obtained for the following clinical factors: has metastatic spread; experienced pain at follow up; experienced nausea at baseline or follow up; and spent days in bed last two weeks at baseline and follow up. Patients with head and neck cancer accounted for 8.8% of the study population, although separate analyses were not reported for them.

Guadagnoll and Mor [24] in a study of 413 active cancer chemotherapy outpatients, reported that over 90% of the sample required help with some type of personal, instrumental, or administrative activity. Assistance with heavy housekeeping, shopping, and completion of forms and paperwork were the most commonly reported issues. Almost 27% of those requiring help reported that their needs were unmet. Males, sample members reporting poor physical functioning, and patients with children at home reported a greater level of need. In a different article focusing on needs assessment data collected from 217 cancer and family members who were already receiving agency services, Mor et al. [25] noted that patients experienced a variety of needs within the physical and instrumental activities of daily living categories, and also with administrative tasks. Age, duration of disease, education, income, gender, marital status, living arrangements, and pain status were correlated to degree of need within categories.

Family caregivers (unpaid people who help with physical care or coping with the disease process) also experience special needs. Hileman et al. [26] reported on information provided by 492 home caregivers. They identified six need categories: psychological, informational, patient care, personal, spiritual, and household. They noted that the establishment of specific programs and services to meet the identified and unmet needs of the caregivers should be a priority, and suggested that frequent reassessment of caregiver needs is necessary.

## Outcomes of Care

Historically, oncologic studies have focused on endpoints such as survival, local control, response rate, and reports of toxicity. For purposes of this chapter, we focused on quality of life and functional status assessment in head and neck cancer patients, two areas that are under-emphasized in traditional clinical studies but receive more attention in the context of health services and outcomes research. (Another important outcome priority from the health services perspective, the costs of care, will be reviewed separately in the next section.) Given the location of these tumors, such outcomes are clearly important. Prior research has demonstrated the adverse impact of severe disfigurement and dysfunction on the recovery time and psychological status of patients with head and neck cancer.[27,28]

It should be emphasized that baseline and intervention factors can have a profound effect on the outcomes of care. Attempts to better quantitate outcomes needs to be integrated with strategies that reproducibly and reliably quantitate patient selection factors and assess the expertise and completeness in which a

therapy or other maneuver is performed. In this regard, Weymuller et al. proposed a computer-based surgical staging and operative data form for Tl, T2, T3, and T4 cancers of the following sites: oral cavity, oropharynx, hypopharynx, supraglottic, glottic, and subglottic larynx, to facilitate standardization of clinically-related data across study sites [29]. These and related issues are comprehensively discussed in a prior chapter by Pfister and Ruchlin.[30]

*Quality of Life/Functional Outcome: Methods*

Gotay and Moore have critically assessed the quality of life literature applicable to head and neck cancer.[31] Morton provided a useful historical perspective on quality life assessment in this disease.[32] Quality of life and functional outcome are not synonymous. Quality of life is the broader concept, and functional issues are commonly assessed as part of quality of life measurement. These areas will be jointly discussed here, given the overlap between the two, and that many of the methodological challenges in their measurement are similar.

Historically, quality of life and function have been referred to as "soft" outcomes, as opposed to the "hard" outcomes such as change in tumor measurements or survival. A major challenge has been to develop state of the art instruments which reliably and reproducibly quantify these outcomes. Several valid head and neck cancer-specific instruments exist. Browman et al. [33] developed and validated an instrument -- The Head and Neck Radiotherapy Questionnaire -- for clinical trials to measure radiation-related acute morbidity and quality of life from the perspective of the patient. List et al. [34] developed a simple, clinician-rated instrument, called the Performance Status Scale for Head and Neck Cancer. This reliable tool includes three subscales (understandability of speech, normalcy of diet, eating in public), and has demarcated important functional differences when challenged with a broad spectrum of head and neck cancer patients. Baker [35] developed a functional status scale with good validity, reliability, and discriminant validity, that focused on shoulder/upper body mobility with elbows straight, chewing, swallowing, drooling, taste, dry mouth, eating, speech, breathing, appearance, pain, and fatigue. The University of Washington Quality of Life Head and Neck Cancer questionnaire [36] is a self-administered instrument with validity and reliability comparable to the Karnofsky Performance Status and the Sickness Impact Profile. However, it was better able to detect clinical change than these latter two instruments. The Functional Assessment of Cancer Therapy (IFACT) scale [37] and the European Organization for Research and Treatment of Cancer (EORTC) quality of life tool [38] are both comprehensive instruments that combine a core quality of life instrument with a head and neck specific module. The above psychometric and functional information can be integrated with data obtained through speech and swallowing physiologic testing and audiometry.

The perspective used in any assessment is an important consideration. Bjordal et al. [39] used the EORTC core and diagnosis-specific module, Kamofsky Performance Status, and the Spitzer Quality of Life index to assess patient and

clinician perspectives on quality of life one to six years after treatment for head and neck cancer in a cross-section of 50 patients. The patients reported lower quality of life and more post-treatment side effects compared with their physicians' assessment. Deciding which instruments to use is another challenge. The goal is to obtain complete but not redundant information, while minimizing patient burden and extraction time. D'Antonio et al. [40] applied general and disease-specific measures to the same group of 50 adult patients who were three months to six years after major surgery. They found that the two types of instruments contributed unique information about quality of life. Different functional status measures, however, correlated well with each other.

*Quality of Life/Functional Outcome: Examples*

Many studies have begun to incorporate such methodologies into their performance and reporting. Selected examples are provided below.

Jones et al. [41] used the EORTC quality of life core and head and neck module questionnaires to assess the quality of survival for five groups of patients, categorized by the type of surgical procedure they had undergone. The procedures included total laryngectomy (n--15), pharyngolaryngoesophagectomy (n=5), cranlofacial procedure (n=l 1), other operations (n=9), and patients with disease recurrence (n--8). They analyzed the following outcome domains: pain, fatigue, physical symptoms (gastrointestinal and other), functional activity, psychosocial symptoms, overall physical condition, and overall quality of life. Their research indicated that laryngectomees and other operation patients reported relatively few problem areas, but patients with disease recurrence described difficulties in all the domains.

In another study using EORTC quality of life measures, Bjordal et al. [42] assessed quality of life in 204 surviving patients who had previously participated in a randomized trial that compared conventional radiotherapy (2 Gy, 5 days a week) to a hypofractionated regimen (2.35 Gy, four days a week). They noted that patients in the hypofractionated arm reported similar or better quality of life compared to patients in the conventional arm. Patients in both groups described a high level of symptoms, such as dryness in the mouth and mucous production. Clinical and sociodemographic variables did not explain variance in social function, emotional function or fatigue, except for the type of surgery performed (defined as none, minor or major) which significantly influenced patients' emotional function.

Ground et al. conducted a retrospective analysis of 167 patients with head and neck cancer evaluated during 1983 and 1989, and assessed the causes and mechanisms of pain using World Health Organization (WHO) guidelines [43]. Eighty-three percent of the patients had pain caused by cancer and/or treatment (28%); debility lead to pain in 4%; and 7% reported pain unrelated to cancer. When a WHO analgesic ladder approach was applied, severe pain was experienced only during 5% of the observation period.

Neck management is a central issue in the treatment of head an neck answer. Shone and Yardley [44] assessed the outcome of 46 patients who had undergone

neck dissection more than six months previously using a preliminary questionnaire followed by interview and examination. They noted that 46% of those employed prior to the operation stopped working because of problems with their shoulder, and 36% complained of moderately severe or severe pain related to the shoulder. They also reported that the amount of pain could not be correlated with age, gender, side of the operation in relation to handedness, physical build, or whether the patient had been treated with radiotherapy.

Suits et al. [45] assessed wound healing problems, quality of speech, degree of aspiration, and need for shunt revision among 39 patients who underwent near total laryngectomy. Severe aspiration was a complication in eight patients, necessitating the reversal of the shunt in four. Severe aspiration and poor voice outcome were most likely in patients who experienced a postoperative pharyngocutaneous fistula.

Hoyt et al. [46] assessed the impact of radiation therapy on the voice quality of patients with squamous cell cancers of the head and neck. Based on data collected on 25 patients, they noted that those with early laryngeal tumors showed improvement in intelligibility, percent of sound voiced, and sound perturbation. Those with nonlaryngeal tumors had no change in the above noted parameters.

The Psychosocial Adjustment to Illness Scale (PAIS) and the Mayo Clinic Postlaryngectomy Questionnaire were used by DeSanto et al. [47] to assess quality of life in patients receiving total laryngectomy (n=111), near-total laryngectomy (n=-38), and partial laryngectomy (n=23). They noted that responses to the PAIS questionnaire did not differ between the total and near-total laryngectomy groups with the exception of the work domain, where, interestingly, the near-total laryngectomy group experienced greater difficulty with their work than the patients who had undergone total laryngectomy. They also reported that the overall adjustment of both groups was less favorable than that of a comparison group with nonlaryngeal cancer. The presence of a permanent tracheostome was especially important in this regard. Indeed, the authors concluded that the presence of a stoma may have a more negative impact on adjustment postoperatively than voice alteration.

Langlus et al. [48] evaluated the functional status and coping of patients with oral or pharyngeal cancer before and after surgical management. The Sickness Impact Profile and Sense of Coherence scales were used. Psychosocial and physical functioning, as well as the functions of recreation/pastimes, work, home management, eating, and sleep/rest were impaired both two to four and 12 months after treatment. Functional limitations were related to more extensive surgery and also to less successful coping; however, the obtained values were spread over a wide range, with large individual differences. Pauloski, Logemann, and colleagues used an audio recording, the sentence version of the Fisher-Logemann test of articulation, and a modified barium swallow with flouroscopy to evaluate speech and swallowing in a group of surgically treated patients with tumors located in primary sites similar to the Langlus study.[49] They found that the speech and swallowing function largely plateau at one to three months post surgery in these

patients, with little improvement in the next nine months. Of interest, most rehabilitation was concentrated into the first postoperative month.

Kreitler et al. [50] developed their own questionnaire to assess life satisfaction in head and neck cancer patients, of all stages and grades of tumor. Questions such as "How much satisfaction and enjoyment of life do you generally feel?", and "How will things be with you in the future?" were asked together with 49 multiple-choice items assessing satisfaction with one's overall state of health, concern with one's health, fears concerning health, coping with health problems, work, economic state, family life, parenthood, communication with one's partner, sexuality, getting help from others, social life, and entertainment. They noted that life satisfaction was related to most domains but not to health or optimism.

Reporting on the responses of 30 patients to questionnaires addressing various psychosocial variables including anxiety, depression, social support, health locus of control, adjustment to illness, illness-related behaviors, and compliance, McDonough et al. [51] noted that psychosocial distress reduced compliance as measured by missed appointments. However, this same distress was associated with better compliance with medication recommendations.

Flap reconstruction is widely used in the management of head and neck cancer, but outcomes besides flap survival are important, especially given their significant cost. Anthony et al. [52] assessed the use of radial forearm free flaps for pharyngoesophageal reconstruction in 22 consecutive patients. The patients had undergone primary (n=3) or secondary reconstruction (n=19) after total laryngectomy. Circumferential reconstructions were done in 13 patients and patch reconstructions in nine patients. They reported that all 22 flaps survived and none of the patients died. Although seven reconstructions leaked, all but one closed spontaneously. In the 16 patients with an intact base of tongue, 14 had no dysphagia and were on a regular diet, with two remaining on a regular liquid diet. Compared with controls, patients with a radical free-flap reconstruction had similar loudness with soft and loud speech, comparable fundamental frequencies, but increased jitter. Speech intelligibility was judged by untrained listeners for six patients with circumferential reconstructions who had later undergone tracheosophageal puncture with placement of a Blom-Singer prosthesis. They rated speech intelligibility as excellent for four of the patients and good for another two.

## Costs of Care

Five types of economic analyses appear in the literature: cost-identification, cost-effectiveness, cost-benefit, willingness-to-pay, and production function-oriented analyses. The first four are used in assessing the economic attributes of a program/intervention, while the fifth focuses on how the services/care is delivered. It should be emphasized that considerable non-financial information, some of which was highlighted in the prior section, is necessary to perform and interpret these studies. While charges are frequently reported as cost proxies, they do not reflect

the actual costs. This is a common methodological deficiency of most of the studies that are described below, to which readers should be alerted.[53]

A cost-identification analysis comparing esophagomyotomy and pneumatic dilatation for treatment of 123 patients with idiopathic achalasia was undertaken by Parkman et al.[54] Although achalasia is not an oncologic problem per se, the procedures evaluated have potential application in patients with head and neck cancer. Costs were identified from a societal perspective, and included estimates of hospitalization and physician costs, medications, home health care, and special diets; nonmedical costs resulting from treatment, such as transportation and family care; and indirect morbidity costs associated with loss of work days. Cost of treatment were estimated based on actual payments for services rather than provider charges. The total average cost of treatment per procedure was $19,000 for esophagomyotomy and $3,654 for uncomplicated pneumatic dilatation. For these two options, direct medical costs accounted for 80.1% and 85.7%, no-medical costs accounted for 0.5% and 1.9%, and indirect costs accounted for 19.4% and 12.4%, respectively. On cumulative cost analysis which took into account additional therapy or re-treatment, esophagomytomy was still 2.4 times more expensive than pneumatic dilatation.

Helmus et al. reported on the feasibility of same-day stay surgery for selected head and neck procedures. Among 200 operations reviewed, 22 were resections of usually T1, oral cavity lesions. Overall, 82% (164/200) of patients did not require an overnight stay, with an estimated savings of more than $23,000 (1990 dollars) in bed charges.[55] Benninger et al. [56] compared symptom-directed selective endoscopy to panendoscopy in 100 patients with upper aerodigestive tract tumors. They reported total billings (charges) of $308,100 if all patients had undergone complete evaluations. A selective symptomatic approach would have yielded a total billing of $205,314, which is a reduction per patient of $1,028. Excluding esophogram and bronchial washings, but performing selective endoscopy and chest x-ray would result in a saving of $751 per patient.

Three studies compared the cost of different treatment options (endoscopic cordectomy [EC], hemilaryngectomy [HL], or radiation therapy [RT]) for T1 glottic larynx cancer. In each case, charges were used as a proxy for true costs, direct medical costs were the primary focus, comparability of disease was based on T stage only, and each treatment option was assumed to yield similar outcomes. The analysis by Mittal et al. [57] was limited to 33 patients (18 RT, 15 HL) treated during 1980 and 1981, and included treatment and transportation costs. They found that the average per patient cost of RT was $2,920 compared to $6,415 for HL. Myers et al. [58] also found RT to be less expensive than HL ($32,588 versus $35,616 per patient), although EC was the least expensive option ($12,956 per patient). Their figures were in 1992 dollars, and also incorporated the anticipated cost of subsequent salvage treatment. Cragle and Prandenburg [59] determined average hospital and physician charges for the immediate treatment period for six patients, three each treated with EC or RT. Current Procedural Terminology (CPT) billing codes for 1990 were utilized. This assessment approach yielded average

costs of $5,944.67 and $14,150.87 for EC and RT, respectively. The results of these studies are difficult to compare given that the quoted dollar amounts are not discounted to the same year. Even when this is done, however, marked variability in cost estimate for a given modality persists (e.g., RT). Many potential explanations exist for this variability. The known geographic variation in the cost of medical procedures is one consideration.[60]

No comprehensive cost-effectiveness and cost-benefit analyses relevant to head and neck cancer were identified, although some authors used the term cost-effectiveness in their articles. In the previously mentioned study by Cragle and Brandenburg [59], objective voice assessment data was provided on 11 laser cordectomy patients from their institution which appeared comparable to published data for a similar group of patients with early tumors treated with RT, thus allowing the reader to infer cost-effectiveness. Blair et al. retrospectively assessed the cost of antibiotic prophylaxis for 192 patients undergoing clean head and neck surgery. Wound infections occurred in 10.1% (10/99) patients who did not receive antibiotics. The excess charges accrued to each patient who developed a postoperative wound infection was in excess of $36,000 (1992 dollars), whereas the cost of administration of antibiotic prophylaxis per 100 patients ranged from $14,660 to $49,600 depending on the antibiotic used.[61] Harrison et al. [62] provided long-term socioeconomic data on 29 patients with squamous cell base of tongue data treated with primary radiation-based therapy (including interstitial implant) from 1981-1990. Most patients retained their pretreatment income and employment status. Such data is fundamental to cost-benefit analyses.

McNeil et al. [63] conducted a utility designation study, a starting point for a willingness-to-pay analysis regarding the management of T3 glottic larynx cancer. Attitudes toward speech versus survival were assessed among 37 healthy volunteers (12 firefighters and 25 upper management executives). Approximately 20% of participants favored radiation over total laryngectomy, despite the prospect of a 20% decrease in cure rate. The investigators demonstrated that patients' attitudes toward morbidity are important, and survival is not their only consideration. Of note, the socioeconomic status of the study group (67% were upper management volunteers) is atypical for a head and neck cancer population, and healthy people do not always express the same sentiments toward illness as individuals with the disease.

Most of the production function-oriented studies seek to identify the "best" way to treat an illness. In our literature review, however, best was not decided on explicit economic criteria. Randomized trials [64,65] and meta-analyses [66] evaluating different approaches to the same clinical problem are illustrative of the idea.

Decision analysis is a methodology increasingly used to address management dilemmas applicable to patients with head and neck or other types of cancer. For example, Weiss et al. [67] used decision analysis to assess three major strategies (observation, radiation, neck dissection) in the treatment of the N0 neck in patients with squamous cell head and neck cancer. They concluded that observation is appropriate if the probability of occult cervical metastasis is less than 20%, but for

higher probabilities, treatment of the neck is warranted. Other topics that have been the focus of a published decision analysis include the management of stage I floor of mouth cancer [68], stage III pyriform sinus cancer [69], and glottic larynx cancer. [70,71] It should be emphasized that these models are quite dependent on their underlying assumptions, and conclusions can vary markedly depending on them. For example, Van der Donk et al. [71] used utility assessment measures (time tradeoff, standard gamble, rating scale, and direct comparison) to derive quality-adjusted-life expectancy (QALE) scores for radiation versus total laryngectomy for T3 laryngeal cancer. They found that QALE scores were lower in former cancer patients compared to groups of clinicians or the general populations. Different utility methodologies frequently yielded different treatment preferences.

Studies have also appeared focusing on the appropriateness of additional service utilization in providing care. Boysen et al. [72] questioned whether routine follow-up beyond the third post-treatment year was necessary. Baatenburg de Jong et al. [73] argued that ultrasonography combined with ultasonographic fine-needle aspiration is an accurate diagnostic test for malignant nodal involvement vis-a-vis computed tomography or magnetic resonance imaging, and may potentially change indications for elective and therapuetic neck treatment.

## Work-Force Issues

While many surgeons since the mid-17th century have fostered the development of head and neck surgery as a specialty, the Society of Head and Neck Surgeons was not founded until 1954.[74] Among its many professional activities is assessing the adequacy of the supply of head and neck surgeons. Using data on members of the American Society for Head and Neck Surgery and the Society of Head and Neck Surgeons, Close and Miller [75] developed a mathematical model, based on physician age and entry and exit patterns, to predict future supply. Applying this model to the 1994 rosters of both organizations, they reported that the total number of head and neck surgeons should decrease slightly from 1,109 in 1994 to 1,028 in 2014. This small numerical decrease was deemed not to be important, and the authors concluded that a "steady-state" supply of head and neck surgeons should prevail over this 20 year period.

Recognizing the current interest in having 50% of the physician workforce in the area of primary care, Bailey [76] noted that the need for a 37% decrease in the otolaryngology-head and neck surgery workforce has been discussed. He critiqued the "50% solution" and believes that it is economically-based rather than "reality-based" in terms of medical science. He emphasized the need for strategic planning to address workforce concerns. Some material needed for the use of any strategic planning was provided by Crumley [77] based on his survey of postgraduate fellows in otolaryngology-head and neck survey. Seven hundred forty-four questionnaires were mailed out, and 344 were returned. Respondents felt that although there were enough fellowship training positions, improvements in the

quality of the training programs were needed. Seventy percent of the respondents indicated a preference for a Certificate of Added Qualifications from the American Board of Otolaryngology for credentialing and validation of their fellowship training.

Johnson et al. [78] sent out 1,045 surveys to the membership of the American Society of Head and Neck Surgery and the Society of Head and Neck Surgeons to ascertain attitudes on current developments and also the prevalence of self-designated burnout. Data on the 395 respondents indicated a mean age of 48 years, and an average workload of 66 hours per week. More than 70% of work was devoted to patient care of which 30% to 50% was spent on the management of patients with head and neck cancer. Thirty-four percent indicated that they felt "burned-out", 27% indicated frustration with disease, 67% noted frustration by government, and 58% indicated frustration by the economics of medical practice.

## Discussion

The review presented in this chapter indicates that the available health services research literature provides numerous insights for policymakers and researchers regarding head and neck cancer patients and their management. There remain, however, many opportunities for further investigation. We documented the incidence and the prominent risk factors for these diseases. Access to care remains an issue requiring a change in physician attitudes and, more importantly, new federal and state policy interventions. More research is needed to identify effective and efficient prevention strategies. Similarly, outpatient and family caregiver needs deserve more attention 1 if one wishes to minimize expensive institutional care.

A substantial literature on quality of life and functional status measurement exists to support outcomes research in this area, although the economic evidence reported to date has significant methodological limitations. Nevertheless, work has been done indicating appropriate techniques of economic analyses [79-81], and data sets exist to support such research. The production function-related research, with the addition of economic evaluations, should provide useful information for consideration in the development of practice guidelines.

A start has been made in assessing the adequacy of the head and neck workforce, although all the identified research focused on surgeons. Attention to the other medical professionals providing care and management services is needed. Similarly, as managed care firms continue to grow and mature, their impact on workforce supply and demand merits study.

Considerable attention has been given to the extent of Medicare payments for cancer patients by stage of diagnosis [82]. Data have been published for lung, female breast, prostate, colon/rectum, and bladder cancers. Comparable work is needed for head and neck cancer.

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