CHAPTER 2

REVIEW OF LITERATURE

2.1. Scientific Approach to Policy Research

Evaluations are integral parts of health care delivery, and professionals play a vital role in current health care management. For example, pharmaceutical practice and policy research is an applied field of research that deals with issues impacting pharmaceuticals, pharmacists and pharmacy systems. Applied research methodologies in health care management research have been instrumental in the growth of health care delivery. This in turn helps in the growth of the applied scientific knowledge base to aid evidence based medicines decisions; relevant to patients, providers, payers and policy makers. With increasing complexities of health care delivery, research has become the cornerstone in safety and efficacy pharmacological management. The stages of healthcare delivery policy research may be followed, in the same sequence as other experimental research, as research problem, research hypotheses, research design, research methodology, statistical analysis, research report, summary and conclusions.  

2.2. Outcomes Research

International society for Pharmacoconomics and Outcomes Research (ISPOR) defined outcomes research as “the scientific discipline that evaluates the effect of health care interventions on patient-related, if not patient-specific, clinical, humanistic, and economic outcomes”. It addresses the clinical, economical and humanistic aspects of health care interventions in the prevention, diagnosis, treatment and management of a disease. Outcomes research represents a diverse field that addresses several arenas, such as cancer control, cost or health related quality of life (HRQOL).
In 1987, the United States National Cancer Institute supported outcomes research initiatives within the Surveillance, Epidemiology and End Results (SEER) program. The results of national level efforts have culminated in the migration of outcomes research into mainstream clinical research. It has become popular among professional organizations related to health care delivery, for example the American Society of Clinical Oncology and the American Society of Therapeutic Radiation Oncology, have separate outcomes research committees. The United States National Cancer Institute has established an Outcomes Research branch, which has mission like ‘multidimensional measures of patient function, quality-of-life and health status, preference-based utility measures and measures of economic costs of cancer-specific interventions’. Different arenas of outcomes research can be classified in to three main levels: Macro level (the level of an entire nation). Meso level (at the level of a larger population), and Micro level (at the level of the individual patient).

2.2.1. Macro-level research

Macro-level research is synonymous with descriptive studies and population surveillance. Targets include cancer-related outcomes, cost and health care utilization, as well as racial, ethnic and geopolitical population health determinants. Recently, these methods were complemented with analytic studies and HRQOL assessment that has been made possible in population-based studies. Population surveillance studies may explore the use of macro level research.

2.2.2. Meso-level research

Meso-level research distinguishes itself from its macro-level counterpart by greater complexity of its sub arenas. Meso studies attempt to make inferences about the impact of disease characteristics, patterns of screening, detection or diagnosis. They address the effect of health services utilization on various disease-related outcomes. Relative to macro-level research, sample sizes usually
are smaller. Meso-level studies can be subdivided into effectiveness, variability, disease impact, clinical modeling and program evaluation studies.

2.2.3. Micro-level research

Micro-level outcomes studies address all aspects of direct patient clinician decision making. They are intervention and disease specific. They may attempt to devise tools that monitor or predict outcomes. Others may be descriptive or may consist of simple risk factor analyses. Finally, HRQOL represents a central ingredient of micro-level studies. Specific examples of tools aimed at standardizing patient physician encounters at the micro level include the TNM staging system which has been refined to reflect disease specific considerations.

Outcomes data can be complemented by randomized controlled trials (RCTs). Moreover, outcomes data may be presented independently or used in various modeling techniques. The resulting outcomes can be applied to the individuals for counseling. Alternatively, by observing the trend in certain territories, the data can be used for entire nations. The outcomes of research can be extrapolated so that it has gained the momentum and a popular status in recent times. Wide access to information technology and data sharing efforts between researchers represent some collaborative that will continue to fuel the exponential growth of outcomes research in times to come. The good understanding of disease processes, effects of screening, detection and interventions will allow refining the techniques and hopefully will culminate in better outcomes, fewer HRQOL and lower health care cost.32

2.2.4. Comparative Effectiveness Evaluations

Comparative effectiveness research (CER) focuses on understanding the medication prescribing and medication utilizations among physicians and patients with chronic diseases. This will benefit health care policy making in terms of understanding how physicians and patients make more informed decisions by knowing patient health outcomes. CER is defined by institute of medicine committees as the generation and synthesis of evidence that compare
the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care. The purposes of CER are “to assist the consumers, clinicians, purchasers and policy makers to make informed decisions that will improve health care at both the individual and population levels”. CER will be a stimulus for the academic, medical and public health committees to develop a research agenda that is responsive to the needs of the clinical community, providing health care professionals with information for clinical decision making.

2.2.5. Outcomes Research-A Holistic Approach to Patient Care

Outcomes research is a holistic approach to patient care. It is multidisciplinary, science combining principles of epidemiology, clinical research, health economics, assessing QOL, and health policy. It also investigates the impact of prevention/treatment on patient’s clinical, economic and humanistic outcomes. The available data for outcomes research include disability, dissatisfaction, discomfort, economic burden, cure, improved survival, recurrence and/or death. The cost involved in managing a disease condition involves cost for drugs, doctor’s visits, investigations, hospitalization, surgery, radiotherapy, professional and service charges and such other expenses. For example, Confederation of Indian Industry, Pharma and Biotech Committee September 2005 reported, the overall cost of managing a disease includes cost of drugs 15%, diagnostics 24%, cost of hospitalization 17% and the remaining as other expenses. Health economics is the comparative analysis of different health interventions in terms of clinical effectiveness, their costs and consequences with the aim of facilitating informed decision making on how to use available resources to maximize outcomes.

Patients experience the diagnosis of cancer as one of the most traumatic and revolutionary events that has ever happened to them. Independent of prognosis, the diagnosis brings with it a change in a person’s self image and in his or her role in the home and workplace. The cancer patient feels that he or she, and not is diseased. A holistic approach can address such issues in cancer care.
2.3. Economic Outcome of Breast Cancer Diagnosis and Treatment

For women given a diagnosis of breast cancer there are many costs. In addition to the direct medical costs, the cost for time away from family, work, and social activities, the cost of ADRs management, as well as the costs involved in restoring the changes in body image, and the interpersonal and existential challenges of living with a cancer diagnosis.

Medical technology is expensive in most fields of clinical medicine especially in oncology. This has resulted in escalation of treatment costs, affecting affordability and accessibility of treatment to patients. According to the Centers for Medicare and Medicaid Services (CMS), in USA during 1965 approximately 5% of the United States gross domestic product (GDP) was spent on health care. Since then, growth in health expenditures has consistently escalated growth in GDP. In 2004, health expenditures were approximately 16% of GDP, and it is projected that by 2014 the health care expenditure will be nearly 20% of GDP. The increase in allocation of significant amount reflects changes in socio demographics of diseased population, accompanied by changes in intensity, volume, and costs of services provided to patients. Since 1965, there has also been a steady increase in the proportion of national health expenditure that has been financed through public funds.42

Pharmacoeconomics is the scientific discipline that assesses the overall value of pharmaceutical health care products, services, and programs. It adopts and applies the principles and methodologies of health economics to the field of pharmaceuticals and pharmaceutical policy. It also addresses the clinical, economic and humanistic aspects of health care interventions in the prevention, diagnosis, treatment and management of disease. Pharmacoeconomics thus provides information critical to the optimal allocation of health care resources.20

Neal et al, (National Institute of Health) estimated that the total cost of cancer care in the United States in 2005 was $209.9 billion. Direct medical costs
including inpatient and outpatient care, drugs, and devices accounted for $4 billion of this total, $17.5 billion was attributed to indirect morbidity costs (i.e., lost productivity), and indirect mortality costs (i.e., lost productivity due to premature death) accounted for $118.4 billion. Drugs used in cancer treatment of patients account for a high percentage of medical drug expenditures in hospitals and outpatient clinics. Cancer-related therapeutics represents a significant cost in both the inpatient and outpatient setting.\textsuperscript{42}

The burden of cancer care in patient’s perspective include direct and indirect costs and this have a strong impact on patient’s decisions on spending for cancer care. The diagnosis of cancer, along with subsequent related care, imposes a number of restrictions on patients like physical, emotional, and financial. Caregivers of adult patients face similar pressures; the cancer patient’s reduced ability to work coupled with the need for the healthy potential wage earners to care for the patient often severely limits the incomes of these families. Of course, the impact of the cancer diagnosis extends beyond the patient, by changing the lives of spouses, children, and other family members and loved ones.

Costs are calculated to estimate the resources that are used in the production of a product or service. The costs associated with cancer care can be classified as direct or indirect. Direct medical costs are the primary costs to measure. These are the medically related inputs used directly to provide the treatment. Direct medical expenditures include items such as the cost of prescription drugs, procedures, diagnostic assessments, and hospitalization, as well as fees for professional services. Indirect costs are secondary costs incurred by cancer treatment but not applied directly to medical care. Secondary costs of cancer care are often lower than direct costs, and are the responsibility of the patient which imposes a considerable burden, in the absence of co payment like insurance and subsidies by the governments. Indirect costs include wages lost due to loss of employment or reduced hours of work. The patients on pharmacological management show fatigue and the other adverse effects of
treatment, which makes them lose opportunity of learning. Indirect costs of cancer care also include the costs of transportation to and from treatment locations, as well as the expense of securing child care if necessary. In addition to transportation costs, these patients and their families must often pay for lodging near the treatment center, as well as food and other incidentals. Patients are often too ill to travel even short distances independently and even patients with strong support networks struggle to secure transportation to and from frequent medical appointments.

Clark et al conducted a study to examine clinical outcomes and cost associated with the use of ondansetron and granisetron in the management of chemotherapy induced nausea and vomiting in Indiana university medical center and found that granisetron is cost effective when compared with ondansetron.\textsuperscript{43} Howard et al conducted a study to assess clinical effectiveness of docetaxel and prednisone in hormone refractory prostate cancer. In this retrospective study, the researcher compared the median survival with docetaxel and prednisone with the results of prior clinical trials which indicated there was no improvement in survival.\textsuperscript{33}

Radice and Redaelli reported that around 10 million individuals develop cancer each year globally. They projected that this number is expected to increase to 15 million in 2020 and the total economic burden of cancer should be in the range of $US 300-400 billion in 2001 (about $US 100-140 billion as direct costs and the remainder as indirect costs [morbidity and mortality]. According to the National Institute of Health (NIH), the total cost of cancer was estimated at $US 156.7 billion in 2001 in US ($US 56.4 billion as direct costs, $US 15.6 as indirect morbidity costs, and $US 84.7 billion as indirect mortality costs). They opine that breast cancer can be projected to account for about one-fifth/one-fourth of the total cost of cancer. The cost of treatment for breast cancer in developing countries is $\leq 5\%$ of that in developed countries.\textsuperscript{44}
2.4. Humanistic Outcome (Quality of life) after Breast Cancer Treatment

The diagnosis of breast cancer continues to generate fear and turmoil in the lives of women and their families. Prevalence studies of psychological distress indicate that one out of every 3 newly diagnosed patients experiences significant difficulty in acceptance and adjustment of the situations. There exist full of confusions, uncertainties, anxiety and distress once a woman is diagnosed to have breast cancer. Along with these, the aggressive treatment procedures adopted for the treatment of breast cancer, surgery, chemotherapy and radiotherapy, including different investigational procedures leads the patient and the family members to some chaos. The heavy economic burden adds to the agonies due to the diagnosis. All these have an influence on the quality of life (QOL) of patients.

QOL is one measure of focus when evaluating the patient centered (humanistic) outcomes. Various combinations of drugs and treatment modalities are employed according to the severity of the disease condition in breast cancer and the treatment adopted will have an impact on the quality of life of these patients. QOL is considered as a measure of success of treatment to certain extent. The increase in breast cancer cases in recent times has led to raise the burden on health care project of an individual patient, in the absence of support from co-payers like health insurance, charitable insurance and governments. This moves health care providers to explore the problem and search for practical solutions that will positively add some value in the areas of cancer research and treatment. WHO defines QOL as individual’s perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person’s physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their life environment.
Health related quality of life (HRQOL) is now considered as important end point in cancer clinical trials. Assessing QOL in cancer patients would contribute to improved treatment outcomes. Among the QOL studies of cancer patients, breast cancer has received most attention because of the following reasons. First of all the number of breast cancer patients are increasing. Each year over 1.1 million fresh cases are diagnosed globally and 0.41 million are dying due to breast cancer. The early detection and treatment can improve survival and QOL study will positively contribute to those who are taking care of those patients. The breast cancer patients lose their personal identity itself, especially those who are undergoing mastectomy. So it is important to study the QOL of life for such patients. In a descriptive study of published literature on nonmedical outcomes in breast cancer patients, the most frequently reported outcomes were HRQOL.46

Safee et al conducted a cross sectional study to measure the quality of life of breast cancer patients under chemotherapy at Namaz Hospital ward in shiraz city, Tehran, using EORTC QLQ C 30 questionnaire. The mean age of patients was 48.27±11.42 and QOL total score 64.92±24.28. All symptoms scales had reverse association with quality of life except appetite loss and diarrhea (P>0.05). The results of the regression analyses showed that only grade of tumor, occupational status, menopausal status and financial difficulties were statistically significant in predicting patient’s QOL. The study established the strength of the relationship between clinical and socio-demographical factors and breast cancer patients’ QOL and concluded that psychological and financial support for women experiencing breast cancer diagnosis may improve quality of life.47

Jeanne et al conducted a study to assess cognitive function, QOL and psychological distress after surgery for early breast cancer, before initiation of adjuvant treatment during the year 2004-2006. In this population based study in the country of North Jutland, Denmark among women aging less than 60 years, the cognitive function and psychological distress was compared with those of women without the history of breast cancer, using the data collection tool,
EORTC C 30. The study result revealed that there was no significant difference in the neuropsychological tests between the patients and the control group, while there was 3 to 4 fold increased risk of experiencing cognitive impairment in breast cancer patients. QOL and psychological distress also were poor among the patients. They concluded that women diagnosed with breast cancer experience a significant deterioration of their perceived cognitive functioning, quality of life and psychological well being.\(^{46,48}\)

Kandaswamy et al conducted a cross sectional correlative study to measure the influence of spiritual well being on symptoms of distress, depression and other dimensions of quality of life in advanced cancer patients receiving palliative care in a Hospice in Karnataka state for 3 months in 2010. The visual analogue scale was used were pain, Anderson symptom inventory, hospital anxiety depression scale, functional assessment of cancer therapy-palliative care and functional assessment of chronic illness therapy-spiritual well being. The depression and anxiety were negatively correlated with spiritual well being and spiritual well being was significantly correlated with fatigue, symptom distress, memory disturbance, loss of appetite, drowsiness, dry mouth and sadness. Spiritual well being was positively correlated with all other aspects of QOL. Regression analysis revealed that predictors such as palliative care wellbeing, distress, sadness, mood and enjoyment in life were positively correlated with spiritual well being. The study concluded that spiritual well being is an important factor to consider in cancer palliative care.\(^{49}\)

Dubashi et al conducted a study to estimate the quality of life of young women in a tertiary care hospital of south India using EORTC QLQ C30 and QLQ BR 23 questionnaire. Comparison of QOL issues was carried out among women undergone mastectomy and breast conserving surgery. It was found that the global health status was better in mastectomy group and the arms symptoms were better in breast conserving surgery group. The pain and financial problems were found to be higher in breast conserving surgery group. The functional
scales were high and the overall sexual functioning was lower after surgical treatment for breast cancer.\textsuperscript{50}

Montazeri et al in a study to measure the QOL of breast cancer patients revealed that overall, breast cancer patients perceived benefit from their cancer treatment in long-term. The impact of breast cancer diagnosis and its treatment on QOL of women with breast cancer was examined. Patients reported outcomes showed that the functional and symptoms scores were poor following treatments.\textsuperscript{46}

It is important to address the psychological issues of women after breast cancer diagnosis. Alawadi and Jude conducted a study to evaluate the quality of life of Kuwaiti women with breast cancer and found that there was relatively high in number that met the criterion for good functioning on the functional scales. It was concluded that there is a need for an evidence base to boost national health education about psychosocial prognosis in cancer. In view of the poor performance on the symptom scales, clinicians treating Kuwaiti women with breast cancer should prepare them to attend acute toxicities of treatment and address fatigue. There is a need for, the institutional support for establishing psycho-oncology service to address psycho-social issues.\textsuperscript{51}

Pandey et al conducted a study to find out the determinants of QOL of among breast cancer patients undergoing treatment with a curative intent in southern part of Kerala and found that factors such as patient education, spouse’s support, employment status and financial stability have been influencing the QOL of women with breast cancer.\textsuperscript{52}

There are many instruments available to evaluate QOL of breast cancer patients. Each one has to select appropriate tool for particular stage of treatment. Levine et al conducted a comparative study among patients of actively undergoing treatment and those who have completed the treatment in order to measure the QOL outcomes of patients. The study revealed that the BCQ and Karnofsky questionnaires were appropriate instruments to demonstrate differences between the groups (P <0.001). Hence, they suggest that the BCQ is a valid and
responsive method of assessing treatment-related morbidity in patients receiving adjuvant chemotherapy for stage II breast cancer.\textsuperscript{53}

Increasing knowledge and use of health status and QOL assessment in clinical research, clinical practice, and policy analysis has initiated a debate over the relative merit of generic versus disease-specific measures. Generic health status measures are those that purport to be broadly applicable to types and severities of disease, across different medical treatments or health interventions, and covering demographic and cultural subgroups. HRQOL is a broad term covering five categories of concepts, including duration of life, impairments, functional states, perceptions, and social opportunities. These are health related to the extent that they are influenced by disease, injury, treatment, or policy. Generic measures may provide operational definitions of several concepts summarized by a single index value or in a profile of interrelated scores.\textsuperscript{54}

QOL assessments have found acceptability among physicians, nurses, and psychosocial staff for several reasons. QOL assessments benefit breast cancer patients because they provide insights into life domains affected by breast cancer that are usually not addressed, including a patient’s mental health, emotional well-being, family and social relations, and abilities to maintain a career, uphold finances, and pursue leisure activities. This knowledge is significant because many breast cancer patients stress that QOL is just as important, if not more important, than quantity of life. Experiencing the effect of breast cancer treatment on a patient’s QOL has been a central clinical and research agenda. For the past quarter century, psychosocial and emotional concerns have been addressed in intervention research of women with breast cancer.\textsuperscript{54}

The overall benefits of QOL assessments include their use in preventive intervention and their potential to inform clinicians about the patient’s illness as well as how certain treatments may affect the QOL of that patient. Jacobsen et al. report that an understanding of QOL also improves communication between
physicians and patients. Evaluation of the advantages of QOL assessments has led the National Institutes of Health and the National Cancer Institute to conclude that QOL measures should be incorporated into research studies when possible.\textsuperscript{55}

### 2.5. Clinical Outcomes

Clinical outcome of a disease and/or treatment are the medical events that occur as a result of disease or treatment. Examples are cure, symptom free survival, stroke, disability, hospitalization so and so forth. Clinical outcomes are usually measured by survival analysis. The survival of cancer patients may depend on many factors including patient’s characteristics and disease characteristics.

Kuru et al conducted a study to find out the predictors of survival. They found that Pathological lymph node status, stage, grade, and estrogen receptor status are the predictors of survival after surgery and the development of metastasis. They also suggested that solitary bone metastasis has a more favorable prognosis than multiple bone metastases. The study indicate that compared to visceral metastasis, skeletal metastasis has a more favorable prognosis.\textsuperscript{56}

Brunk reported that adding radiation therapy after lumpectomy reduces the risk of recurrent breast cancer within 10 years by nearly 15%. Results from the long-term analysis demonstrated that radiations reduces the overall chance of dying from the disease within 15 years by nearly 4%.\textsuperscript{30} Clinical studies indicate that breast cancer patients treated with breast conserving surgery (BCS) without radiotherapy are at a greater risk of recurrence and mortality than the patients on BCS and radiotherapy.\textsuperscript{20}

Jack et al conducted a study to compare the efficacy and safety of anastrozole oral with tamoxifen orally administered for 5 years, as adjuvant treatment for postmenopausal women with early-stage breast cancer. There were 24522 woman-years of follow-up in the anastrozole group and 23950 woman-years in the tamoxifen group. In the study population, there were significant
improvements in the anastrozole group compared with the tamoxifen group for disease-free survival (hazard ratio [HR] = 0.91, 95% CI 0.83—0.99, P=0.04), time to recurrence (0.84, 0.75—0.93, P=0.001), and time to distant recurrence (0.87, 0.77—0.99, p=0.03). For hormone-receptor-positive patients, the results were significantly in favor of the anastrozole treated patients for disease-free survival (HR 0.86, 95% CI 0.78—0.95, P=0.003), recurrence period (0.79, 0.70—0.89, P=0.002), and distant recurrence period (0.85, 0.73—0.98, P=0.02). These data confirm the long-term superior efficacy and safety of anastrozole over tamoxifen as initial adjuvant therapy for postmenopausal women with hormone-sensitive early breast cancer.57

There is growing evidence that the omission of breast radiotherapy after breast conserving surgery in elderly women may compromise survival. The Oxford overview of trials of adjuvant radiotherapy with 24,000 patients reported that, for those managed by postoperative radiotherapy in addition to surgery, added 5% to overall survival at 15 years.58

Reed et al reported that surgery is beneficial in improving the survival and local control of the disease, even in elderly women (70-75 years). The surgeries in elderly women have no effect on survival due to the increasing frequency of mortality due to other causes.59

Accurate and reliable decision making during treatment planning in breast cancer management can help in the selection of suitable surgery and therapy. This can optimize patient management through the different stages of the disease. Lundin et al evaluated the accuracy of neural network in predicting 5, 10 and 15 year breast cancer survival. Eight variables were entered as in put to the net work; namely tumor size, axillary nodal status, histological type, mitotic count, nuclear pleomorphism, tubule formation, tumor necrosis and age. Axillary lymph node status, no versus positive predicted 5 year survival with specificity of 71% and a sensitivity of 77%. The authors reported that neural net works can be important tools for cancer survival prediction.60
Gajalakshmi et al conducted a population based study of breast cancer patients in order to find survival rate. The mean follow-up time was 43 months. The overall Kaplan-Meier survival analysis measured at 1, 3 and 5 years were 80%, 58% and 48% respectively. The corresponding figures for relative survival were 81%, 61% and 51%. The multi factorial analysis of prognostic factors using a proportional hazards model showed statistically significant differences in survival for subjects in different categories of age at diagnosis, marital status, educational level and clinical extent of disease. In the geriatric patients the survival was less, when compared to younger women. Unmarried women displayed poor survival (37.4%) at 5 years than married women (50.0%). The survival rate among those who had more than 12 years of education was higher (70%) at 5 years in comparison to illiterate subjects (47%). An inverse relationship was observed between survival rates and clinical extent of disease. The study result emphasizes the need for research to determine feasible public health approaches, allied to coordinated treatment facilities to control breast cancer in India.\textsuperscript{61}

**Summary**

This chapter dealt with an extensive review of the topics related with outcome research, including economic, clinical and humanistic outcomes and few studies conducted in this area.