Employing PROs in Economic Evaluation Studies on Treatments of Cancer Patients with Prescription Medications

Von der Wirtschaftswissenschaftlichen Fakultät der
Gottfried Wilhelm Leibniz Universität Hannover
zur Erlangung des akademischen Grades

Doktorin der Wirtschaftswissenschaften
- Doctor rerum politicarum -

genehmigte Dissertation

von

M.Sc. Jia Liu

geboren am 08.08.1981 in Chengdu, China

2011

Referent: Prof. Dr. J.-Matthias Graf von der Schulenburg

Koreferent: Prof. Dr. Wolfgang Greiner

Tag der Promotion: 14. Dezember 2011

Abstract

This thesis employs Patient-reported Outcomes (PROs) to conduct empirical research on the treatment of cancer patients with prescription medications. One is a macro-level study which examines the association of factors related to cancer prescription medication use, Health-Related Quality of Life (HRQoL) and prescription medication expenditures in the United States. The other one is a meso-level study which examines patient satisfaction and subjective experiences of treatment with breast cancer hormonal medications.

Firstly, this thesis helps establish a framework for understanding HRQoL and the real spending on cancer-related medications among cancer patients by using survey data. It was pointed out that cancer medication use was associated with significant impairment of HRQoL. Differences in the impairment also exist across groups of different socioeconomic status (SES). Additionally, total and out-of-pocket prescription medication expenditures were significantly affected by patient characteristics such as age, region, insurance status, chronic conditions and HRQoL. Secondly, this thesis gives a better understanding of breast cancer patients' subjective experiences and satisfaction with hormonal medications by using patient self-reported data. It revealed that musculoskeletal symptoms or nervous system problems have a significantly negative impact on patient satisfaction, while long-term medication treatment or currently consistent use of medication has a significantly positive impact on patient satisfaction.

Overall, this thesis provides a new benchmark for these values which can be applied to the management of cancer medications, as well as a reference point for future research and baseline into clinical practice.

Key words:
Cancer, patient-reported outcomes, prescription medication expenditures

Zusammenfassung

Diese Arbeit befasst sich mit der empirischen Untersuchung von Krebstherapien mit verschreibungspflichtigen Medikamenten unter Verwendung Ergebnismessung aus der Sicht des Patienten (PROs). Die Arbeit ist untergliedert in eine Studie auf Makroebene, in der die Beziehung zwischen der Verwendung von Krebs verschreibungspflichtigen Medikamenten, Gesundheitsbedingte Lebensqualität (HRQoL) und Verschreibungspflichtigen Medikamentenausgaben in den Vereinigten Staaten von Amerika untersucht wird. Weiter wurde eine Studie auf Mesoebene durchgeführt, welche Patientenzufriedenheit und subjektive Erfahrung mit Brustkrebshormonbehandlungen untersucht.

In dieser Arbeit wird ein System aufgebaut um HRQoL und die tatsächlichen Ausgaben für Krebsbezogene Medikamente bei Krebspatienten von Umfragedaten zu verstehen. Es zeigte sich, dass die medikamentöse Krebsbehandlung mit einer signifikanten Einschränkung der HRQoL in Zusammenhang steht. Außerdem zeigte sich, dass diese Einschränkung der Lebensqualität je nach sozioökonomischem Status variiert. Zusätzlich werden die Gesamt- und Privatausgaben für die Behandlung mit verschreibungspflichtigen Medikamenten signifikant durch Charakteristika des Patienten wie Alter, Region, Versichertenstatus, chronischen Krankheiten sowie HRQoL beeinflusst. Im zweiten Teil dieser Arbeit wird ein besseres Verständnis für subjektive Erfahrungen und Zufriedenheit der Brustkrebspatienten vermittelt von die Daten aus der Sicht des patienten. Es wird deutlich gemacht, dass Symptome des Bewegungsapparats und Probleme des Nervensystems maßgeblich die Patientenzufriedenheit negativ beeinflussen, während Langzeitbehandlungen oder regelmäßige Medikamenteneinnahmen diese positiv beeinflussen.

Zusammenfassend bietet diese Arbeit eine neue Bezugsnorm für diese Werte, welche in der Planung von Krebstherapien angewendet werden, sowie als Referenz für weitere Forschung und Basis für die klinische Praxis dienen kann.

Stichwörter:
Krebs, Ergebnismessung aus der Sicht des Patienten, Verschreibungspflichtigen Medikamentenausgaben

Acknowledgements

I would like to take this opportunity to acknowledge and express my appreciation for the individuals who contributed in some form to the creation of this thesis.

First I am heartily thankful to my supervisor, Prof. Johann-Matthias Graf von der Schulenburg, for the supervision, guidance and incredible support during all these years. This thesis would not have eventuated unless Prof. Schulenburg helped me with the analysis and the thesis revision from introduction to conclusion. I would also like to give my grateful thanks to other committee members: Prof. Ulrike Grote, Prof. Wolfgang Greiner, especially Dr. Anne Prenzler, for their patience and help in completing this thesis.

In addition, my analysis could never be possible without the help from Dr. Thomas Mittendorf, Kathrin Damm, Kristijan Kahler and Eric Wu for all the knowledgeable advices and help. I owe an immense gratitude to Prof. Andreas Wagener, Prof. Hans-Gerd Ridder, Prof. Heidrun Hoppe-Wewetzer, Prof. Patrick Puhani and Prof. Hendrik Hakenes, who are wonderful lecturers in the courses I took.

I appreciate the assistance from Sabine Quary, who took care of lots of my personal errands while I was away from Germany. Also a special thanks to Christine Steinmann, Dr. Ute Lohse, Dr. Sebastian Braun, Simone Krummaker, Dr. Meik Friedrich, Dr. Christoph Vauth, Christoph Schwarzbach, Jaqueline Knigge, Fang Chen, Trevor Stewart, Chuthaporn Ngokkuen, Wei Chen and Chen Chen for their kindly help and support.

I owe my deepest gratitude to my parents and parents-in-law for the unconditional love and support. I would like to express my gratefulness to my husband Dr. Changyi Zhou for his constant patience, understanding and always being there for me. He has been so supportive all these years and helped a lot with the revision of the thesis draft.

Lastly, I offer my regards and blessings to all of those who supported me in this thesis.

Table of Contents

List of Tables

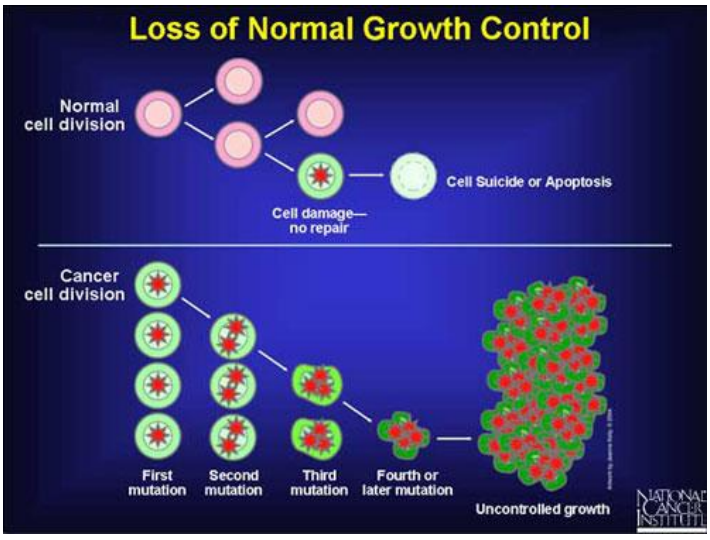
List of Figures

Chapter 1: Introduction

1.1 Study Background

Cancer is a group of diseases in which abnormal cells divide out of control and are able to invade other tissues.[1] All cancers begin in cells. The genetic material (DNA) of a cell can become damaged or changed, resulting in mutations that affect normal cells to grow and divide.[1] When normal cells are damaged and cannot be repaired, they are eliminated by apoptosis. However, cancer cells continue to multiply in an unregulated manner. See Figure 1.

Figure 1: Cell Division



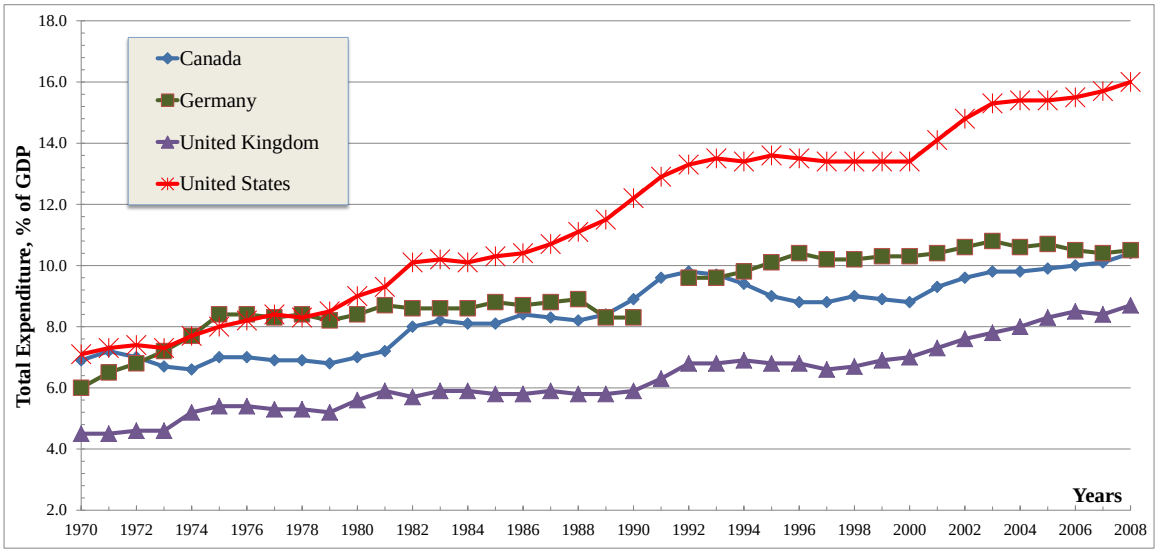
Cited from: National Cancer Institute[1]

The extra cells may form a mass of tissue called tumor. Tumors can be divided into benign (non-cancerous) and malignant (cancerous) tumors. Benign tumors can often be removed, and recurrence is rare in most cases. Usually, benign tumors are not life-threatening. Cells in malignant tumors may spread to surrounding tissues, nearby lymph nodes, or other parts of the body. The cancer that spreads from one part of the body into other parts of the body through the blood and lymph systems is called metastasis or a secondary tumor.

The year 2008 World Cancer Report released by the International Agency for Research on Cancer (IARC) estimates that cancer is the leading cause of death worldwide in 2008.[2] Globally there were over 12 million new cases of cancer diagnosed, and 7 million deaths from cancer.[2] In addition, the incidence of cancer continues to increase; by the year 2030 there will be 27 million incident cases of cancer and 17 million cancer deaths.[2]

In the worldwide, cancer cases are rising in prevalence as well as incidence resulting in a growing need to allocate financial resources to this sector of the health care system. The rising healthcare costs leave a growing economy a heavy burden of cancer.

Figure 2: Total Health Expenditures on Health, Percentage of GDP



All the data are collected from OECD Health Data 2010: Statistics and Indicators.[3]

Figure 2 shows that healthcare costs in some developed countries have been increasing for decades. The proportion of Gross Domestic Product (GDP) devoted to health care has dramatically increased which reflects changes in volume, intensity and service costs provided to patients. In 2008, the expenditures on healthcare totalled percentage of GDP were 10.4% for Canada, 10.5% for Germany, 8.7% for the UK and 16% for the United States. Compared with other countries, the U.S. poses the most dramatic increase.

In the United States, cancer is the second leading cause of all deaths, which accounts for nearly one of every four deaths.[4] According to the National Institutes of Health (NIH)'s estimation, the costs of cancer treatment have increased substantially in the past two decades.[4] See Table 1 for the cancer costs in the last decade in the U.S.

Table 1: Cancer Cost Figures in the U.S. in Last 10 Years

Year	Overall Annual Cost for Cancer ($, Billion)	Direct Medical Cost ($, Billion)	Indirect Morbidity Costs [1] ($, Billion)	Indirect Mortality Costs [2] ($, Billion)
2001	156.7	56.4	15.6	84.7
2002	171.6	60.9	15.5	95.2
2003	189.5	64.2	16.3	109.0
2004	189.8	69.4	16.9	103.5
2005	209.9	74.0	17.5	118.4
2006	206.3	78.2	17.9	110.2
2007	219.2	89.0	18.2	112.0
2008	228.1	93.2	18.8	116.1
2009	243.4	99.0	19.6	124.8
2010	263.8	102.8	20.9	140.1

Notes:

[1] Indirect morbidity costs are the costs of lost productivity due to illness.

[2] Indirect mortality costs are the costs of lost productivity due to premature death.

All the data are collected from American Cancer Society, Cancer Facts and Figures 2001 - 2010.[4]

The overall annual costs of treating cancer consist of direct and indirect medical costs. Compared with direct medical costs (e.g., inpatient, outpatient and emergency room care, drugs, and facilities), indirect medical costs, especially mortality costs (i.e., lost productivity because of premature death), take up more than half of overall cost. Taking year 2010 as an example: among the $263.8 billion overall costs, 39% was attributed to direct medical costs, 7.9% was attributed to indirect morbidity costs (i.e., lost productivity because of illness), and 53.1% was attributed to indirect mortality costs. However, from year 2001 to 2010, the increasing rate of direct medical costs (Δ47.0%) is much faster than that of overall annual costs (Δ35.8%) and indirect medical costs (Δ29.5%) (inflation adjusted to year 2001). It is also anticipated that cancer costs may grow faster than overall medical expenditures in the near future.[5]

In order to manage cancer, medications dispensed to patients are considered as a primary method of therapy. As a result, medication costs represent the largest portion of direct medical expenditures to society. Dr. Florence Tangka of the Centers for Disease Control and Prevention (CDC) and her colleagues used five years data from the Medical Expenditure Panel Survey (MEPS) to estimate the cancer cost in the United States.[6] They estimated that the total yearly medical cost of cancer in the U.S. nearly doubled from $24.7 billion in year 1987 to $48.1 billion which was the average cost from year 2001 to 2005. As a proportion of all cancer-related costs, cancer-related prescription drug spending also increase from 1.8% to 6.1%. For Medicare, the overall spending increase 47% ($210 billion vs. $309 billion) from year 1997 to year 2004, while the spending on cancer-related drugs rose 267% ($3 billion vs. $11 billion) during the same period.[7] USA Today examined "how the high prices of new cancer medications - up to $10,000 a month for a single drug - are causing alarm among patients and insurance companies".[8] It pointed that "according to the report released by pharmacy benefit manager Express Scripts, the cost of cancer medications increased by almost 16% in 2005, compared with a 3% increase for other treatments".[8] This report also found that in 2005 the average cost of a 30-day prescription for cancer medications was about $1,600.[8]

The strong upward rise in cancer drug prices and spending has given both patients and health economists great cause for concern. The high cost of cancer treatment leads to financial difficulty for patients and their families, even including those covered with health insurance. One recent survey finds that 25 percent of individuals with cancer report consumption of all or most of their savings to treat cancer.[9] Even among insurance beneficiaries, 22 percent report consumption of all or most of their savings to treat cancer.[9] In addition, in some cases, the prices of cancer drugs rise faster than the health benefits associated with them, which attracted health economists' attention.[7] Therefore, cancer outcome research becomes more and more vitally important now than ever. The purpose of cancer outcome research is "describing, interpreting and predicting the impact of cancer interventions, as well as other effects with regard to the outcomes that are crucial to decision makers".[10] Such outcomes include not only traditional biomedical outcomes (e.g., survival, disease-free survival), but also patient-reported outcomes (PROs) (e.g., health-related quality of life (HRQoL), patient satisfaction and economic burden).[10]

1.1.1 Patient-reported Outcomes (PROs)

As the differences in efficacy benefit for the patients between cancer therapies become smaller, there is a growing recognition on "the patient's perspective" in cancer treatment decision making. If we know the value people attach to the health improvement they receive from different interventions, it could be helpful to determine how to efficiently provide more or less of the outcomes that people desire or not desire.[11] Patient-reported outcomes (PROs) are collected directly from patients. This information can describe the clinical course of cancer, help select optimal treatment, or assess the effectiveness of interventions and the overall burden of cancer. Hence, PROs of cancer patients as an important therapeutic endpoint is increasingly being given a high priority in clinical trials.

Many U.S. research and policy-related developments value the importance of PROs in the cancer sphere. The National Cancer Institute (NCI) has designated it as a Strategic Objective – Using PROs to ensure the improvement of the quality of life for cancer patients, survivors and their families.[12] One of the American Cancer Society (ACS)'s 2015 goals for the nation is improving the quality of life of all those affected by the disease.[13] Thus, it would be crucial to measure the cancer and its treatment's impact on quality of life (QoL) from cancer patients' standpoint.

The U.S. Food and Drug Administration (FDA) also grant that new drugs must be both safe and effective for approval. They encourage using PROs in clinical trials to indicate whether a new drug or treatment is working and how well it is working. The additional information from PROs can support the approval and also label claims for a new drug. In Feb. 2006, the FDA issued a draft guidance document on the use of PRO measures in industry-sponsored studies to support drug-labeling claims. The guidance published by FDA points out that "a PRO is a measurement of any aspect of a patient's health status that comes directly from the patient, including the symptom status, functional status (e.g., daily living, social functioning), health-related quality of life (HRQoL) and patient satisfaction".[14]

1.1.1.1 Health-related Quality of Life (HRQoL)

In practice, the patient's assessment of HRQoL is considered the most prominent end point or outcome measure to show changes from the patient's perspective.[14] Assessing HRQoL is more complex than some other PROs and may provide information about treatment outcomes in multiple domains. Therefore, the patient's assessment of HRQoL is an essential indicator of treatment effectiveness and may influence recovery goals.[15]

The important dimension of health is quality of life (QoL). The World Health Organization (WHO) in year 1995 defined QoL as "the individual's perceptions of their position in life in the context of the culture and value system in which they live, and in relationship to their goals, expectations, and standards".[16] QoL refers to every facet of a patient's life. The patients' view of their quality of life may also include the aspects of life that are not health related. Thus, QoL is not an appropriate outcome for evaluating a medical product. In contrast, HRQoL can complementally provide valuable information on the patient's self-health perception about treatment impact. For this reason, the FDA permits HRQoL claims on the label of certain drugs.

Assessing HRQoL is most commonly used to test the safety and efficacy of new therapies in randomized trials by special QoL instruments, which include physical, psychological (including emotional and cognitive), and social domains. These multidimensional HRQoL measures can assess the impact of the disease on each of these domains. In addition, these measures can be used to assess both the positive impact of the treatments and the negative impact from side effects associated with the treatments.[17]

Due to the importance of HRQoL in assessing both the burden of cancer and benefits of treatment, over the past ten years, lots of instruments developed to assess HRQoL have been made available to clinicians and researchers. To be accepted as a scientific measure, a HRQoL questionnaire must confirm validity, reliability, and sensitivity to clinically important changes, otherwise the assessments of symptom relief and quality of life will be hampered.[18] In general, two types of HRQoL measures are classified: health status measures that describe the health state of an

individual along various attributes of health for a specific period or at a particular time;[19] utility measures that provide numerical assessments of health states. Table 2 lists the most frequently used HRQoL instruments in cancer treatment.

Table 2: Commonly Used Health-related Quality of Life (HRQoL) Instruments in Cancer Outcome Researches

	HRQoL Instruments
Health Status Measures	
Generic Measures	SF-36 (Medical Outcomes Study 36-item Short Form Health Survey) Karnodsky Performance Scale (KPS)
General Cancer Measures	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C-30) Functional Assessment of Cancer Therapy-General (FACT-G) Functional Living Index-Cancer (FLIC) Spitzer Quality of Life Index (SQLI) Cancer Linear Analog Scale (CLAS)
Cancer-specific Measures [1]	Functional Assessment of Cancer Therapy-Lung (FACT-L) Functional Assessment of Cancer Therapy-Prostate cancer (FACT-P) Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer (EORTC QLQ BR23) Functional Assessment of Cancer Therapy-Biologic Response Modifiers (FACT-BRM) Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane) Breast Chemotherapy Questionnaire (BCQ) Functional Assessment of Cancer Therapy-Fatigue (FACT-F) Functional Assessment of Cancer Therapy-Anemia (FACT-An) Functional Assessment of Cancer Therapy-Endocrine Symptom (FACT-ES) Brief Fatigue Inventory (BFI) Mental Health Inventory (MHI) Rotterdam Symptom Checklist (RSCL) Symptom Distress Scale (SDS) Brief Pain Inventory (BPI) Menopause-specific quality of life Questionnaire (MENQOL)
Utility Measures	Visual Analogue Scales (VAS) Time Trade-Off (TTO) EQ-5D (EuroQoL) Quality of Well-Being Scale (QWB) Health Utilities Index (HUI)

Notes:
[1] Here only list most commonly used cancer-specific instruments. For specific form of cancer, here only list lung cancer, prostate cancer and breast cancer, which rank the top 3 of the U.S. national expenditures for medical treatment for the cancers.

Health Status Measures

Generally, health status measures are typically subdivided into generic and specific measures. For assessing both the burden of cancer and benefits of treatment, these measures can be classified as generic measures, general cancer measures and cancer-specific measures.[17]

The generic measures are performed for general use. It is suitable for a wide range of diseases and health conditions of patient groups. Patients' overall life is dissimilar under alternative medical interventions and the extent of the difference is reflected by measuring general health status. These measures help to quantify the relative impact of interventions on the patients with different diseases.[20] Therefore, measuring general health stats is important. The Medical Outcomes Study 36-item Short Form Health Survey (SF-36) is most frequently applied to cancer treatment. It has 36 questions covering eight health domains.

General cancer measures assess individuals' functioning and well-being as pertains to cancer, but without reference to a specific type of cancer.[17] These measures address the general areas of HRQoL relevant to all forms of cancer. Thus, they cannot be used in patients with specific types of cancer. Examples of general cancer measures are the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ C-30) and the Functional Assessment of Cancer Therapy-General (FACT-G).

The cancer-specific measures emphasize the specific form of cancer (e.g., breast cancer), such as the Functional Assessment of Cancer Therapy-Breast cancer (FACT-B). In addition, they also assess individual's functioning and well-being as pertains to a specific treatment for cancer (e.g. chemotherapy), or a particular impact of cancer on HRQoL (e.g. fatigue, depression). Examples are the Breast Chemotherapy Questionnaire (BCQ) and the Hospital Anxiety and Depression Scale (HADs).

In terms of the application of the three types of measures introduced above, generic measures are broadly applicable and allow for comparisons among disease groups and population. Thus, they can enable comparison of the burden of cancer versus the burden associated with other conditions.[17] While when assessing QoL of specific patient groups, cancer-specific measures are more sensitive and responsive to the changes than generic measures.[18] However, there is no single instrument incorporating all aspects of HRQoL, therefore it is typical that one of these generic measures is combined with one or more cancer-specific measures to measure baseline

health status, comparative health status, and effectiveness/outcomes of clinical intervention.

Utility Measures

Utility measures assign numerical values for health states from 0 to 1, where 0 indicates death and 1 indicates the best health state.[20] Utility measures are able to integrate morbidity and mortality. They consist of two main components: a) the definition and description of health states; b) the measurement of the preference for each health state.[21] These components can be applied in direct preference-based measures and indirect preference-based measures.

Direct preference-based measures assess the preference for a health state, including Visual Analogue Scales (VAS), Standard Gamble (SG) and Time Trade-Off (TTO). VAS is a method used to measure preference for health outcomes. Patients are asked to mark the position of their current health state on the 10 cm line, and the position that corresponds with their feelings as well.[20] The results of VAS give an indication of the ordinal ranking of the health outcomes. SG estimates patients' preferences under uncertainty, which contains a risk of death or some other outcomes.[20] TTO also attempts to measures patients' preferences under certainty. Patients are asked to indicate that they prefer to choose one year in perfect health or one year in impaired health. Both SG and TTO are practical on most populations, and TTO could be used to replace to the SG.[20] While, VAS is more commonly used. By using these direct preference-based measures, patients could provide global assessments of the net effect of treatment on their HRQoL, including positive treatment effects and negative side effects. However, these measures have been found to be less responsive to health change than standardised health status measures.[22]

Indirect preference-based measures describe the health status of a subject by using a multi-attribute health status classification system and a scoring system to value health status, such as the EuroQoL (EQ-5D), the SF-6D, the Quality of Well-Being Scale (QWB) and the Health Utilities Index (HUI). Usually, these measures only have a few questions. For example, patients using the EQ-5D questionnaire have to answer six questions in two sections. One section consists of five questions to assess QoL in

the domains of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The other section gives an expression of their current health statuses via the VAS.[20] In practice, due to the ease of use, the indirect utility measures are widely used.[22]

In health economics, the health state utilities are usually combined with survival estimates, then aggregated across patients to generate quality-adjusted life years (QALYs).[21] QALYs can be used in cost-utility or cost-effectiveness analyses to assess the extent of the benefits gained from healthcare interventions.[23] When combined with the costs of providing the interventions, the comparisons between interventions can be made.

Differences between Health Status Measures and Utility Measures

Unlike health status instruments, utility measures are patient preference-based measures of health states. In health economics, utilities are principal values that reflect an individual's preferences for different health outcomes.[21] From the patients' point of view, their preferences are the important criteria to assess whether the treatment can be considered efficient. In addition, economists also suggest extracting the patient preference affected by an intervention.[20] Utility assessments use a single number to summarise HRQoL. This number not only reflects the health status of the patient, but also reflects the patients' preferences for treatment process and outcome.[24] Therefore, utility measures are the preferred outcome measure for modelling the cost-utility analysis to aid in making resource allocation decision.

Due to the difficulties encountered in interpreting the quality of life scores, it is often impossible to use HRQoL instruments directly. However, they can still be useful to be included in an economic evaluation to

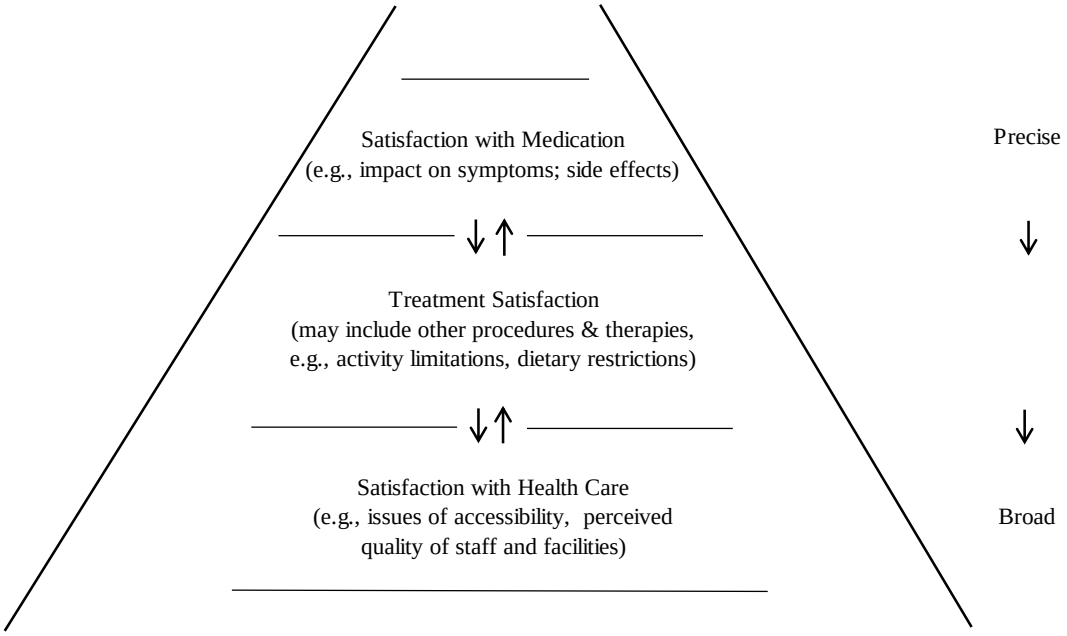
- gain more information about the changes of quality of life with different treatments in specific dimensions;
- ensure that different treatments have identical outcomes in cost-minimization studies;

- classify patients into different health states. Such classifications can be used as a basis for measuring the quality weights to construct QALYs and/or the willingness to pay for health changes.

1.1.1.2 Patient Satisfaction

Patient satisfaction has been of increasing interest over the past few decades. It is an important patient-reported outcome measure for estimating the extent to which health care service meets patients' needs and expectations.[25] Patient satisfaction can be considered as a hierarchy.[26] See Figure 3.

Figure 3: Hierarchy of Levels of Patient Satisfaction



Cited from: Shikiar R, Rentz AM. Satisfaction with Medication: An Overview of Conceptual,Methodologic, and Regulatory Issues. [26] Page 205.

The broadest level of the hierarchy is satisfaction with health care. It covers all aspects of the health care received. The middle level represents global treatment satisfaction. It involves not only patient satisfaction with medication, but also satisfaction with other issues, such as recommendations by the physician about other procedures and therapies (e.g., activity limitations, dietary restrictions, physical rehabilitation), and interaction between physician and patient.[26] Lastly, at the

narrowest end of the hierarchy, it is the satisfaction with the medication received. These levels interact and impact each other.

Patient satisfaction, this type of PRO, is different from other PROs such as health-related quality of life (HRQoL) and self-reported symptoms or functioning. The theoretical basis of patient satisfaction research is found in the planned behaviour theory, which is an extension of the Theory of Reasoned Action (TRA).[26] The most important insight provided by TRA is its attempt to explain behaviour regarding medical care or medication in terms of beliefs about the outcomes of performing the behaviour and the evaluation of each of these outcomes.[26] On one hand, patient satisfaction affects the patient's health-related decision making. On the other hand, it provides the professional health care providers, the researcher and the policy makers with important feedback from patients, and may help to support a claim for a new product.[15]

Patient satisfaction with medical care is considered an indicator of quality of care. It includes a number of factors, such as access to medical staff timely, perceived quality of medical staff and facilities, the patient's experience with regard to the duration or side effects of the treatment, and patient's expectations for receiving effective medical care on time.[26] Currently, many countries or organizations develop corresponding patient-experience measures. For example, the United Kingdom conducts a yearly Survey of Patient and User Experience to report detailed patient experiences in some selected areas such as hospital care.[27] The department of Agency for Healthcare Research and Quality (AHRQ) in the United States has supported and helped to develop the Consumer Assessment of Health Plans.

With regard to cancer, the Comprehensive Assessment of Satisfaction with Care (CASC) is developed to assess the perception of cancer patients with regard to the quality of care received in the hospital.[28, 29] It focuses on patients' interactions with doctors or nurses and mainly evaluates psycho-social interventions that affect patients' quality of life.[29] This questionnaire consists of 60 items regarding doctors' behaviour, nurses' behaviour and services (i.e., the technical, communication and interpersonal skills, availability and co-ordination, waiting time, access, comfort, kindness and helpfulness of other hospital personnel). Each item is aimed at an aspect of care which

is rated on a five-Likert scale ranging from 1 (poor) to 5 (excellent). A scale of overall satisfaction is also included.

Medication satisfaction is increasingly recognized to be essential in determining the efficacy of new therapies. It is a feedback from the patients with respect to the experience of taking the medication and the outcomes related to the medication.[26] It is directly associated with drug adherence and treatment preference, indirectly associated with clinical and HRQoL outcomes. Currently, there are three instruments measuring medication satisfaction regarding cancer drugs. Two are generic instruments. The other is designed for cancer therapy, particularly for intravenous and/or oral anticancer treatments.

Treatment Satisfaction Questionnaire for Medication (TSQM) is a generic instrument, which is designed to assess patient satisfaction with medication for any disease.[30, 31] It is a psychometrically robust and validated instrument and comprises four domains: global satisfaction, effectiveness, side effects, and convenience. In each domain, the scores range from 0 to 100, with higher scores representing greater satisfaction in that domain.

Treatment Satisfaction with Medications Questionnaire (SATMED-Q) is also a generic instrument. It aims at assessing patient satisfaction with chronic drug-based treatment for any disease including cancer.[32] It consists of 17 items on a five-Likert scale from 0 to 4 points (0 = No, not at all, 1 = Somewhat, 2 = So-so, 3 = Quite, 4 = Yes, very much). Mean scores are converted into a scale ranging from 0 (the worst or no satisfaction) to 100 (total or maximum satisfaction). This questionnaire covers six domains (each with 2-3 items) of treatment satisfaction: undesirable effects, medication efficacy, medication ease and convenience, medication impact on daily activities, satisfaction with medical care and overall satisfaction. The SATMED-Q has been proved to be feasible, valid and reliable.

The Cancer Therapy Satisfaction Questionnaire (CTSQ) is designed to measure treatment satisfaction in cancer patients.[33, 34] It could be used in every cancer types and stages, but it is specific to patients receiving oral and/or intravenous anticancer therapies.[34] 21 items are used across seven multi-item domains: expectations of

therapy, feelings about side effects, oral therapy compliance, convenience, satisfaction with therapy, stopping therapy, and reasons for noncompliance. All items are scored on a five-Likert scale. 15 of the items are scored from 1 (the worst response) to 5 (best response). Six of the items are reverse-coded. The CTSQ proves to be with good metric properties.

Overall, patient satisfaction is essential in the studies of cancer outcome. These valuable information, especially the factors affecting satisfaction, could be particularly useful to assess the patterns of care organization, monitor health care delivery, understand the cancer patients' experience on their current treatment, reflect patients' treatment-related behaviours (e.g., drug adherence, treatment preference), and differentiate among alternative treatments. Health care providers and policy makers could be assisted to improve the quality of health services, perform efficient patient and/or cancer treatment management, optimize health expenditure through patient-guided planning and evaluation,[35] then determine the best strategy for cancer interventions.

1.1.2 Economic Evaluation of Cancer Burden

PROs are only partial measures of evaluating cancer burden, because they do not measure the costs spent by individuals or nations in producing these outcomes.[27] Thus, when comparing the costs and efficacy of alternative cancer interventions, economic evaluation is vitally important. There are four types of economic analysis in cancer studies: cost-minimization analysis, cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis. Each follows the same general methodology but differs in the methods used to measure the health outcomes. See Table 3.

Table 3: Types of Economic Analysis

Type of Analysis	Outcome Measure	Costs
Cost-Minimization Analysis (CMA)	None	$
Cost-Benefit Analysis (CBA)	Monetary value (willingness to pay)	$
Cost-Effectiveness Analysis (CEA)	Natural units (e.g., life years saved, quality of life)	$
Cost-Utility Analysis (CUA)	Utility values (e.g., QALYs)	$

The Concept of Cost

From economic perspective, the resources consumed by an intervention reflect its cost.[36] In cancer outcome research, the resources traditionally associated with the health care system are only one aspect of the costs associated with cancer and its interventions.[36] A full analysis of the economic burden of cancer care takes direct, indirect and intangible costs of cancer into account.

Luce et al.[37] explain direct costs in cost-effectiveness analysis of health and medicine as follows:

"Direct costs include the value of all the goods, services, and other resources that are consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it. These costs are often thought of as involving - or potentially involving - a monetary transaction, although it is the use of the resource rather than a monetary exchange that defines the direct cost. Direct costs encompass all types of resource use, including the consumption of professional, family, volunteer, or patient time. Because the intervention (e.g., screening) can affect both current and future resource use and costs, these costs should be considered a stream of resource use that can span time, from a year or less for a simple procedure, to a lifetime for a preventive intervention or a chronic disease treatment regimen."

In brief, direct costs comprise direct health care costs (e.g., diagnosis, laboratory tests, medical facilities, patient out-of-pocket expenses including co-payments), direct non-health-care costs (e.g., treatment-related transportation and child care), and patient time costs (e.g., the time a patient spends to seek care, the time of receiving treatment).

Indirect costs are related to productivity loss due to illness and its treatment. These costs are typically measured by morbidity and mortality-related cancer cost. Morbidity costs of illness refer to the lost or impaired ability to work (e.g., days lost from work, foregone wages). Economic output and the time lost or forgone by the patients' family and friends from usual activities (e.g., income lost by family members,

restricted leisure time) are also considered as the morbidity costs.[38] Those related to the value of future income lost due to premature death are considered as the mortality costs of illness.

Intangible costs are pain and suffering from disease and its treatment, psychological costs (e.g., anxiety, grief), changes in social functioning/daily activities, or other effects on the patient's quality of life. They have no market prices, and are usually measured by the reduction in quality of life.

Economic Analysis

Cost-minimization analysis (CMA) is applied to compare and find the lowest cost among different drug treatments. When conducting a cost-minimization study, all costs (resource expenditures) need to be measured and competing alternatives of drug treatments need to have equal efficacy and tolerability. However, it is rare to use cost-minimization analysis, because effectiveness, utility and safety of interventions must be identical, meanwhile only changes in costs of the intervention are taken into account.

Cost-benefit analysis (CBA) measures the costs and benefits in monetary units of different treatments to decide the least costly way of achieving any positive outcome. The approach is useful since it leads to a simple decision-making rule: if a treatment's net benefits exceed its net costs, then it should be adopted.[39] However, CBA also raises measurement difficulties, because it requires the monetary valuation of health benefits. In practice, it is the most difficult and most criticized analysis.

Cost-effectiveness analysis (CEA) compares the costs and effectiveness of two or more interventions, where only the costs are calculated in monetary units, while the effectiveness is defined by the health benefit or outcome achieved with the intervention and expressed in non-monetary or natural units. This effectiveness is defined by a summary measure that combines quantity of life (mortality) and quality of life (morbidity), weighted by the preference for that quality of life. It is calculated as the difference in costs between two alternatives divided by the difference in health effects.

$$\text{Cost-effectiveness ratio} = \frac{\text{Cost of Intervention}}{\text{Unit of health outcomes}}$$

Here, all outcomes are defined by using natural units, including health endpoints (e.g., a case prevented), survival, quality of life etc. When compared with an alternative, cost-effectiveness ratio represents the incremental cost of obtaining a unit of health effect from a given intervention. However, it is difficult to use cost-effectiveness ratio to compare treatments with different outcomes because the health outcomes are difficult to express in a single effectiveness unit. Therefore cost-effectiveness analysis is best suited to measuring technical efficiency.[40]

Cost-utility analysis (CUA) is a special case of cost-effectiveness analysis. It has its roots in expected utility theory, which describes a normative model of rational decision making under conditions of uncertainty.[39] In cost-utility analysis, effectiveness is measured by a utility score derived from utilities measures.

$$\text{Cost-utility ratio} = \frac{\text{Cost of Intervention}}{\text{\# of QALYs produced by Intervention}}$$

Cost-utility ratio indicates how much cost per quality-adjusted life year (QALY) gained. An intervention with a lower cost to QALY saved ratio is preferred over an intervention with a higher ratio. Cost-utility analysis provides a more complete analysis of total benefits because it takes into account the quality of life that an individual has. Therefore, it is most frequently used.

According to the health economics literature, a QALY measures the performance of medical treatments and interventions, and it encompasses both the quantity and quality of life generated by healthcare interventions. The quantity of life is expressed by survival or life expectancy, while quality of life contains different aspects of people's lives, including health status.[23] A QALY is estimated by assigning every life year a weight between 0 and 1. A weight of 0 reflects a health status that is valued to be equal to being dead and a weight of 1 reflects perfect health.

Economic evaluations involve a comparison of costs and outcomes from alternative uses of resources to improve health. To be useful to decision-makers, the results must also be interpreted by attaching clinical meaning to numerical data. Outcomes take on a variety of forms. For making a meaningful comparison, they need to be measured or valued using the same metric. In economic evaluation, although measuring and calculating cost is fundamental and substantial, the key issue is choosing outcome measure. The suitability of an outcome measure depends on the type of treatment that is analysed as well. For example, chronic diseases are difficult to accommodate in the QALY context, because for them quality of life is a major issue while survival is less of an issue. Treatment of hormonal therapy in breast cancer could be an example of this. Both tamoxifen and Aromatase Inhibitors (AIs) are the most commonly used hormonal medicines for postmenopausal women, the comparison in terms of QALYs seems doubtful since both medicines demonstrate similar effectiveness in terms of survival rate, hence the patient HRQoL/satisfaction/preference for a reduction of side effects might be a more fruitful approach.

1.1.3 The Application of Cancer Outcome Measures

Lipscomb J et al.[41] evaluated the peer-reviewed literature in cancer outcome research, and employed a framework to categorize and characterize the applications of cancer outcome measures. This framework adopted three broad categories: macro, meso and micro-level. The specific explanation is as follows:[41]

- Macro-level analyses, investigating current and potential trends in HRQoL of patients among large population, their satisfaction with the care received and the corresponding economic burden are also attached.
- Meso-level analyses, consisting of a wide range of diversified studies on patient-reported outcomes. Those studies include: randomized trials on intervention efficacy; observational designs on intervention effectiveness; cancer impact (with an emphasis on cancer survival); differences of cancer care utilization, quality of cancer care; clinical decision modeling, economic

modeling (e.g., cost-effectiveness analysis), and evaluation existing interventions to help decision makers.

- Micro-level analyses, emphasizing the performance and quality of cancer outcome measures.

Table 4 presents these three categories of application for cancer outcome measures in detail and illustrates their potential uses in decision making.

Macro-level studies examine population trends in cancer-related outcomes and the cancer burden,[41] such as the changes in cancer-related mortality, morbidity, HRQoL and cost, by state and demographic subgroup. They are intended to provide information to policy makers on formation and research agenda, especially for those meso-level studies.[41]

Meso-level studies collect a wide range of sources like patients, families, payers and providers, agencies and organizations, evaluate their influences to decision making and therefore affect the judgements on the safety, efficacy or cost-effectiveness of the cancer care.[41] Examples of meso-level studies are as follows: a) cross-sectional analysis of prevalence and quality-of-life impact of depression and anxiety among long-term survivors of breast cancer; b) randomized controlled trial comparing impact of two competing hormonal therapy regimens on survival and HRQoL in patients with early stage breast cancer; c) prospective cohort study of individuals newly diagnosed with breast cancer to examine the impact of alternative strategies for initial treatment and follow-up care on HRQoL, satisfaction with care, and economic burden; d) cost-effectiveness analysis of comparison with tamoxifen and with anastrozole (Arimidex®) used in postmenopausal patients to reduce breast cancer morbidity and mortality. Meso-level studies may be used to check the macro-level study hypotheses and results, and also to link the process-outcome to support micro-level specific problem solving.[10]

Table 4: Application for Cancer Outcome Measures

	Domains	Potential Uses in Decision Making
Macro	Population trends in cancer-related outcomes and the economic burden	Informs policy makers with information and the research agenda by revealing successes, shortcomings, and areas requiring in meso-level studies for intensive investigation
Meso	Descriptive and analytical studies to understand the impact of cancer, variation in service use and performance, and effects of interventions on cancer-related outcomes. The examples of examinations are as follws:	Provides specific empirical research findings and recommendations to improve public and private decisions on safety and efficacy of cancer care, coverage and reimbursement, regulation (e.g., product approval and marketing), guidelines, and support micro-level research to assess and improve cancer outcomes
	A. Intervention efficacy (randomized controlled trial)	
	B. Intervention effectiveness (observational investigations on the burden of cancer patients and their families)	
	C. Cancer impact: observational studies analyzing the various effects of cancer on patients (e.g., depression), with an emphasis on cancer survivors.	
	D. Variations in utilication 1. Patterns of cancer care: identify significant population differences during the use of cancer services by cross-sectional or longitudinal studies. 2. Monitoring the quality of cancer care by examining patient satisfaction and adherence.	
	E. Intergrating and synthesizing information on outcomes through 1. Clinical decision modeling to select an optimal intervention 2. Economic modeling, such as cost-effectiveness analysis, cost-benefit analysis, cost-utility analysis. 3. Evaluating existing cancer interventions	
Micro	Use QoL instruments and other tools to monitor and predict outcomes, then help examine patient risk profile and behavioral characteristics, and select intervention.	Improve the quality of the information available for decision making, enhance the communication between patients and their providers.

Adapted from: Lipscomb J, Donaldson MS, Hiatt RA. Cancer outcomes research and the arenas of application.[10] Page 3.

Micro-level studies use outcome measurement (e.g., generic, cancer-specific, and/or domain-specific HRQoL instruments) to truly reflect the quality of cancer care itself by improving the patient-provider communication quality and decision making.[41]

In recent years, there is an increasing interest in using macro-level measures to amend health policy by studying cancer disparities and economic burden against national objectives,[27] because population health has become a principal subject in many developed countries. Several national and international organizations such as the World Health Organization (WHO) and the Organization for Economic Cooperation and Development (OECD), have sponsored national surveillance plans (e.g., the evaluation of cancer control programs).[27] In the United States, some government departments, like the Agency for Healthcare Research and Quality

(AHRQ) and the Centers for Disease Control and Prevention (CDC), have begun to develop national quality reports to help establish the priorities, monitor the improvement, and publicly report these findings by assessing national measurement systems related to cancer or other diseases.[27]

Table 5: Cancer Performance Measures and Applications in Macro-level Studies in the United States

Measures	Definition	Data Source
Biomedical Outcomes	**Clinical Endpoint Measures**	**Provider Sources**
Incidence	1. Total proportion of population diagnosed with cancer	Cancer registries
	2. Rate of newly diagnosed "avoidable" cancers in a year	Cancer registries
Mortality	1. Death rate of cancer	Death certificates
	2. Years of life lost: date of death from disease minus estimated date of death based on average life expectancy	Death certificates
Survival	1. Observed survival in a general population: time from diagnosis to death from cancer	Primarily death certificates
	2. Relative survival: the ratio of the observed survival relative to the expected survival of a similar population group	Primarily death certificates
Quality-of-Life Outcomes	**Patient-Defined Endpoint Measures**	**Patient Sources**
Health Status Measures		
Medical Outcomes Study Short Form 36 (SF-36)	Physical and emotional functioning	Population survey
Responsiveness to patients	Patient experience with care, satisfaction with care	Population survey
Utility Measures		
EQ-5D (EuroQoL)	Mobility, self-care, usual activities, pain/discomfort, anxiety/depression	Population survey
Cancer Cost	**Economic Burden of Cancer Care**	**Patient and Provider**
Direct costs	Health services and out-of-pocket costs attributable to cancer treatment	Population surveys
Indirect costs		
Morbidity costs	Lost productivity due to illness	Population surveys
Mortality costs	Lost productivity due to premature death	Population surveys
Other Indirect costs	Burden on family and individual life style	Population surveys
Intangible costs	Pain and suffering, changes in social functioning/daily activities, anxiety, grief	Population surveys

Adapted from: Clauser SB. Use of Cancer Performance Measures in Population Health: A Macro-level Perspective.[27] Page 144.

Table 5 lists the types of cancer performance outcome, the current or potential applications and data sources used for macro-level studies of cancer care in the United States. As the table illustrates, cancer registries or death certificate data normally captured clinical endpoint measures, such as cancer incidence, mortality and survival. Patient-defined endpoints (e.g., general health status, experience or satisfaction with care) are collected from population survey. In addition, cost information, including

direct, indirect and intangible costs, could also be collected from population survey. The macro application of burden-of-disease measures summarize disease burden for a nation, geographic area, entire population or demographic subgroup.[17] Thus, macro-level studies are helpful in assisting researchers to examine cancer incidence and prevalence in the country, then determine whether certain demographic subgroups are disproportionately affected.

Overall, currently there are three broad categories of applying cancer outcome measures. Macro-level studies aim at a comprehensive view of the population trends in cancer-related outcomes from an economic point of view. Meso-level studies are more purpose specific to investigate the cancer impact and the corresponding interventions. Micro-level studies focus on the use of cancer outcome measures, risk and outcome prediction models, or other measurement, and help enhance the quality of information for patient-clinician decision making.[41] These studies could help understand the outcomes of cancer and its treatment, as well as improve the process of cancer care decision making.

1.2 Study Objectives

Due to the improved treatments, cancer survival rates have greatly increased in the past few decades. In particular, cancer drug therapy plays an important role in the treatment of patients with cancer in all stages of the disease. Although the currently available cancer drug treatments improve the survival and relieve some symptoms to a certain extent, at the same time they also produce some unexpected toxic side effects. It is noted that these side effects cause patients' health-related quality of life (HRQoL) and patient satisfaction with medication to decrease. Therefore, when considering the management of cancer patients, there is an increasing demand of recognition that patient-reported outcomes (PROs) – including treatment-related toxicity, the impact of treatments on HRQoL and patient satisfaction – can convey essentially additional information for assessing the overall burden of cancer and the effectiveness of interventions. In addition, the spending on cancer-related prescription medications increases substantially annually. This causes cancer patients exceptionally affected by high out-of-pocket expenditures and gives health economists a great cause for concern

as well. Thus, it is more important now than ever to understand the pattern of cancer-related prescription drug expenditures. However, the studies assessing cancer patients' PROs and expenditures, particularly with respect to prescriptions are lacking and mostly out-of-date. To fill the void, this thesis attempts to attribute the PROs and expenditures of treatment of cancer patients with prescription medications through two empirical researches.

This first research will use the latest Medical Expenditure Panel Survey (MEPS) data to examine the association among factors related to cancer prescription medication use, HRQoL and prescription medication expenditures in the United States. It is intentionally designed to give a comprehensive and up-to-date understanding of HRQoL and expenditures aiding in managing cancer medical costs. By analysing quality of life data, the study will document how HRQoL is affected after taking cancer prescription medications. By analysing medical expenditure data, the study will document how the source of payments are affected, and help establish a framework for understanding the real medical expenses on cancer-related medications among cancer patients.

The second research focuses on breast cancer. It is conducted to examine patient satisfaction and subjective experiences of treatment with hormonal medications-tamoxifen and Aromatase Inhibitors (AIs). Both medications demonstrate similar effectiveness in terms of survival rate. In addition, currently available QoL studies show that although the side effect profiles of them vary significantly, there are no clinically important differences in overall QoL. Consequently, patient satisfaction is particular useful when differentiating these medications. This study will be based on the patient self-reported data collected from an Internet website www.askapatient.com. It will document what factors impact patient satisfaction with hormonal medications. It is carried out to give a deep understanding of the important issues in treatment decision making for postmenopausal women with breast cancer, and serve as the benchmark for policy makers to improve hormonal medication management.

The expected objective of this thesis is providing a new benchmark for these values which can be applied to the management of cancer medications, as well as a reference point for future research and baseline into clinical practice.

Chapter 2: Impact of Medication on Health-related Quality of Life and Expenditures for Cancer Patients in the United States

2.1 Abstract

Objective: To examine the association of factors related to cancer prescription medication use, health-related quality of life (HRQoL) and prescription medication expenditures in the United States.

Methods: A cross-sectional study was performed using the year 2008 Medical Expenditure Panel Survey (MEPS) data. 392 cancer patients with age of 18 and above were extracted. HRQoL measures were used to provide different perspectives on health status of the patients. These measures included the 12-item Short Form Health Survey (SF-12), the Kessler Index (K-6) and the Patient Health Questionnaire (PHQ-2). Multivariate analyses were conducted to examine how certain patient characteristics were strongly associated with HRQoL and high financial burdens separately.

Results: Cancer medication use was associated with significant impairment of HRQoL. Cancer population reported worse physical or mental health, more serious psychological distress and depression than age-matched non-cancer population. Less education attainment and experiencing chronic conditions were associated with poorer HRQoL. The multivariate analysis revealed that among the cancer patients the adjusted annual mean total and out-of-pocket expenditure associated with medications were $2,572.1 and $597.1, respectively. They significantly increased in elderly and Medicare cancer patients. In addition, patients with lower physical SF-12 scores, higher depression PHQ-2 scores were more likely to accrue higher prescription medication expenditures.

Conclusions: An association with cancer medication use on patient health status and medication expenditures was observed. The study findings provide a comprehensive and up-to-date understanding of HRQoL and the real medical expenses on cancer-related medications among cancer patients.

2.2 Introduction

This section will introduce the background of the study first. Then study objectives and research questions will be presented.

2.2.1 Background

According to American Cancer Society, in the U.S., men have slightly less than one in two lifetime risk of developing cancer; the risk is a little more than one in three for women.[4] Today, millions of people are living with cancer or have had cancer.[4] Some of them were cancer-free, while others still had cancer and may be undergoing treatment. The treatment options for cancer patients are limited, because they depend mainly on the stage of cancer, the age and general health condition of the patients. Surgery, radiation therapy and cancer drugs are the most common cancer treatments. Surgery removes the tumor partially or completely, which depends on the type, size and location of the tumor, and how far advanced the cancer is. It offers the greatest chance for cure for many types of cancer, especially localized cancer. However, when the cancer has spread to other parts of the body before surgery, complete surgical removal is normally impossible. Aiming at these patients, radiation therapy and cancer drugs have been developed. Radiation therapy, also called radiotherapy, uses high-energy rays to kill cancer cells by damaging the DNA in their genes, and make them unable to grow and multiply. The main disadvantage of radiation therapy is that healthy cells are damaged as well during the process. Cancer drugs include chemotherapy, biologic therapy, immunotherapy, hormonal therapy and angiogenesis inhibitors. They can be used in both early and advanced stage, even before or along with surgery or radiotherapy. These anti-cancer drugs are taken orally, injected into the vein (intravenous, or IV), or applied to the skin (topically).

Although the currently available cancer drug treatment improves the survival rate, relieve some symptoms to a certain extent, at the same time they also produce some unexpected toxic side effects, such as damaged healthy cells and tissues, fatigue, fever, chills, nausea and so on. Thus, when considering the management of cancer patients, treatment-related toxicity and the effect of interventions on quality of life are also

taken into account. So far, the majority of outcome researches on cancer drug treatment focus on mortality and morbidity since these outcomes are relatively easy to observe and data are readily available. Studies examining quality of life of cancer patients have shown that cancer drug therapies have a detrimental effect on both short and long-term health-related quality of life (HRQoL). However, these studies were mostly localized to specified cancer population. The national impact of cancer prescription medications on quality of life has not yet been fully examined. Such information is absolutely essential when comprehensively assessing the impact of cancer drugs on patients' health and health care in the U.S.

In addition, cancer patients are particularly affected by high out-of-pocket expenditures. The burden of out-of-pocket expenses is an issue of growing concern to both medical and policy community. One of the key reasons is that spending on cancer-related prescription drugs rises faster than spending in many other areas of health care. Therefore, it is more important now than ever to understand the pattern of prescription drug expenditures. It is noticeable that the elderly are incurring more of the prescription spending than nonelderly; racial and ethnic minorities have lower out-of-pocket medication expenditures than the white population; individuals with lower socioeconomic status (SES) incurred greater health care expenditures. However, very few studies assess cancer patient expenditures on prescriptions. In particular, the studies examined the prescription expenditures associated with cancer among the groups of different age, race/ethnic, or socioeconomic characteristics are limited.

2.2.2 Study Objectives

This study is a macro-level study. It uses the latest public-used data to examine the patient characteristics related to HRQoL and expenditures on prescription cancer medications among adult cancer patients. This study assesses HRQoL, the total and out-of-pocket expenditures attributable to the prescription medications taken by cancer patients. It is intended to give a comprehensive and up-to-date understanding of cancer and cancer prescription expenditures aiding in managing medical costs. By analysing quality of life data, the study will document how HRQoL is affected after taking cancer prescription medications. By analysing medical expenditure data,

especially out-of-pocket spending for medications, the study will document how the expenditures are affected by patient characteristics and health status, and help establish a framework for understanding the real medical expenses on cancer-related medications among cancer patients.

One study objective is to compare HRQoL of a large national sample of cancer patients with age-matched non-cancer patients, then examine the patient characteristics related to HRQoL. Although assessing quality of life is important in cancer outcome research, to date, only a few studies have compared the HRQoL of cancer patients taking prescription medications with that of the non-cancer population. National studies regarding this issue are also lacking. To meet the demand, this study quantifies the national impact of cancer patients taking prescription medications in the non-institutionalized population in the United States with different HRQoL measures. It also explores whether the effects of quality of life differ by patient characteristics, such as age, race or insurance coverage.

The other study objective is to estimate the total and out-of-pocket expenditures on prescription cancer medications, and examine how certain patient characteristics and health status strongly associated with high financial burdens. Although HRQoL also reveals the patients' thoughts about the efficacy of treatment, which may influence their utilization of medical services, relatively few studies have assessed costs and health status associated with cancer patients taking prescription medications.

The expected objective of this study is that by investigating HRQoL and economic burden incurred in cancer patients, especially in a specific group of patients, such information could be helpful for policy makers to determine the best strategy for cancer interventions, and perform efficient patient and medical cost management.

2.2.3 Research Questions and Hypotheses

This study is based on the year 2008 public-used data drawn from Medical Expenditure Panel Survey (MEPS), which is by far the latest and most complete

dataset of this survey. The MEPS is a population-based survey for the U.S. civilian non-institutionalized population, which is designed to provide nationally representative estimates on the health care in terms to utilization, insurance coverage, expenditures, and payment sources.[42] The research questions and their hypotheses are described below.

Research Question one:

"What effects do cancer prescription medications have on the health-related quality of life (HRQoL) of cancer patients?"

The hypotheses to be tested are as follows:

1. Cancer patients taking prescription medications show impaired HRQoL in comparison to non-cancer patients.
2. Elderly cancer patients (65 years of age and older) taking prescription medications experience impaired HRQoL in comparison to nonelderly patients.
3. Cancer patients with less education attainment are associated with impaired HRQoL in comparison to their counterparts.

Research Question two:

"What are the factors associated with prescription medication expenditures among cancer patients?"

The hypotheses to be tested are as follows:

1. Elderly cancer patients incur higher total/ out-of-pocket prescription medication expenditures in comparison to nonelderly patients.
2. Female patients incur higher total/out-of-pocket prescription medication expenditures in comparison to male patients.
3. Whites and non-Hispanics incur higher total/out-of-pocket prescription medication expenditures in comparison to blacks and Hispanics.

4. Patients with lower SES (classified as poor or having low income, uninsured) incur higher total/out-of-pocket prescription medication expenditures in comparison to their corresponding counterparts.
5. Patients with worse physical or emotional health, more serious non-specific psychological distress, or greater tendency towards depression are more likely to incur higher prescription medication expenditures.

2.3 Literature Review

This section will provide a systematically literature review related to this study. In order to make comparisons to the results of this study, an overview of the quality of life (QoL) research on cancer will be presented firstly. Secondly, a comprehensive review of the literature on prescription expenditures for cancer will be provided.

2.3.1 Quality of Life (QoL) in Cancer

Unquestionably, traditional biomedical outcome measures, particularly survival and disease-free survival, remain the central topic in cancer decision making.[43] Nevertheless, when the clinicians must make a choice among available cancer therapies that have similar overall survival outcome, the determination is driven by QoL. The reason is that disease-related symptoms, toxic effects of therapy, and the emotional, functional and socioeconomic effects of living with cancer have profound effects on patients' quality of life. These effects can illustrate if the quality of life is improved or impaired.

Quality of Life between Cancer and Non-Cancer Patients

Separating the effects of cancer on HRQoL from the effects produced by comorbid conditions and other life changes is difficult. Hence, in order to make a comparison, additional data on a comparable sample of non-cancer patients are needed. There are several studies comparing quality of life between cancer patients and healthy subjects.

Baker et al.[44] adopted the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) to estimate the HRQoL of cancer survivors in comparison to a frequency age-matched cohort of non-cancer patients. In this study, cancer survivors had statistically significantly poorer scores than non-cancer patients on all eight subscales as well as on the Physical Component measures (PCS) and Mental Component summary measures (MCS) of SF-36 (all $p < 0.0001$).

Holzner et al.[45] used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) to reveal that compared with healthy controls, chronic lymphocytic leukemia patients received chemotherapy experienced a lower QoL in almost all domains. Moreover, female chronic lymphocytic leukemia patients reported remarkably lower QoL scores in emotional and social functioning than male patients.

Two studies compared the HRQoL of hepatocellular carcinoma patients with the general population. The SF-36 and the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) were used respectively. It was suggested that patients with hepatocellular carcinoma had lower HRQoL scores than the general population,[46, 47] especially in physical, emotional, and functional well-being.[47] In contrast, patients reported better scores in social/family well-being.[47]

Botella-Carretero et al.[48] compared 18 differentiated thyroid carcinoma women with 18 age-matched healthy women using four validated HRQoL questionnaires – the SF-36, the Nottingham Health Profile (NHP), the Profile of Mood States (POMS) and the Visual Analogical Mental Scales (VAMS). When compared with healthy controls, patients taking chronic suppressive levothyroxine therapy presented impairment in total score, emotional, sleep, energy and social domain of the Nottingham Health Profile; mental health, general health and social functioning of the SF-36 ($p < 0.05$ for all comparisons).

Pelttari et al.[49] evaluated the impact of cured low-risk differentiated thyroid carcinoma on HRQoL after long-term follow-up by 15D instrument, which is a generic, 15-dimensional self-administered measurement. The HRQoL data obtained from the patients was compared to that of a large, representative sample of the general Finnish

population. It was found that the mean total 15D scores were similar between patients and control subjects. In dimensions of sleeping, speech and distress, differentiated thyroid carcinoma patients were significantly worse off ($p = 0.001$, 0.002 and 0.012, respectively), but in dimension of discomfort and symptoms, they were better off ($p < 0.001$). Within the patient group, age was the only significant independent predictor of HRQoL at the time of the initial treatment ($p < 0.001$).

A longitudinal study used SF-36 to compare the effect of androgen deprivation therapy on quality of life between men with prostate cancer and healthy men.[50] There were small differences in SF-36 Mental Component Summary (MCS) scores, but androgen deprivation therapy use was associated with declines in general health, bodily pain, vitality, physical functioning, and role limitations because of physical health problems.

Factors affecting Quality of Life in Cancer Patients

Quality of life is the outcome of the disease and its treatment; meanwhile it also highly depends on each patient's demographic and socioeconomic status (SES) characteristics. Generally, demographic characteristics comprise age, gender, race, ethnicity, marital status and residence. SES is largely determined by education, income, insurance etc. Some studies produced a consistent findings suggesting that demographic and SES characteristics are related to the disparities in QoL of cancer patients.

A national survey was performed in Japan to investigate the relationships among cancer patients' SES, distress and their QoL after taking chemotherapy.[51] This study used a semi-structured questionnaire composed of the subscales of the EORTC QLQ-C30 and the FACT-Sp (Spiritual well-being) questionnaire. A significant association between QoL and age, cancer type, occupation, and marital status was found. Specifically, patients having an occupation reported a better QoL in Physical Functioning ($p = 0.014$), but a change in occupation (e.g., layoff, retirement) was negatively correlated with Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, Social Functioning and Financial Impact subscale of EORTC QLQ-C30 and the Spiritual well-being subscale of FACT-Sp (all $p < 0.05$).

Patients having a partner negatively correlated with Emotional Functioning ($p = 0.005$) and Spiritual well-being ($p = 0.038$).

There is a paucity of researches assessing the QoL of patients with various types of cancer in relation to their demographic characteristics and SES.

Penson et al.[52] examined whether socio-demographic and clinical variables are predictive of QoL outcomes of prostate cancer patients. General QoL was measured using the SF-36. Disease-specific QoL was measured by the University of California-Los Angeles Prostate Cancer Index (UCLA-PCI). The health distress scale from the Medical Outcomes Study (MOS) and a scale measuring patient self-esteem were also used to measure general QoL. It was noted that prostate cancer patients with higher annual income had better QoL scores at baseline in comparison to those with lower income. For married patients, emotional well-being and family functioning scores were better at baseline, but family functioning scores declined over the nine month study period. Compared with younger patients, older patients had slightly better baseline performance in several domains of QoL, but experienced greater QoL decrease over time. Likewise, increasing comorbidity was associated with worse baseline general QoL. Furthermore, prostate cancer patients insured by health maintenance organizations (HMOs) appeared to have better QoL than those with certain other types of insurance.

Penson et al.[53] further examined the effect of SES on QoL outcomes in men with prostate cancer by the instruments of the SF-36 and the UCLA-PCI. This study also confirmed that patients of lower SES tend to have worse quality of life at baseline and following treatment for their disease. Specifically, significantly lower baseline QoL scores were found in patients with lower annual income. No relationship was observed between annual income and QoL outcomes over time. Conversely, health insurance status has a unique effect on general QoL outcomes in patients after treatment for prostate cancer.

Another study described QoL in low-income men with prostate cancer.[54] Subjects were drawn from a statewide public assistance prostate cancer program. The 12-item

Short Form Health Survey (SF-12) and UCLA-PCI were used to compare prostate cancer patients with normative age-matched men without cancer from the general population. This study revealed that compared with the age-matched general population controls, the low-income men had worse scores in every domain of prostate-specific and general QoL. It also indicated that among the low-income men, Hispanic ethnicity and income level were predictive of worse physical functioning, whereas only comorbidities predicted mental health.

Knight et al.[55] did a research on prostate cancer by using SF-36 and PCI quality of life measures as well. This study showed that low-educated men experienced worse outcomes in most domains of QoL six months after treatment and less recovery of QoL over two years after diagnosis, compared with high-educated men.

Melmed et al.[56] examined the additional factors such as marriage and education on QoL in patients with metastatic prostate cancer. The outcomes were measured with SF-36. It found a slower rate of physical decline in men who were married, well-educated and more affluent, while emotional decline appeared slightly slower in men with lower than a college education level.

Some studies described whether HRQoL differ by socio-demographic characteristics in breast cancer patients. These studies suggested that women who are younger,[57, 58, 59, 60, 61, 62, 63] married,[63] unemployed,[63] highly educated,[60, 63] or religious,[63] with higher monthly household income,[63] or less comorbidities,[60] had higher QoL. In addition, the psychological well-being domain scored the lowest among domains of QoL.[63] African American women report better emotional well-being and mental health but lower levels of physical functioning than white women.[64, 65, 66, 67]

Likewise, there are two studies that examined how SES affects QoL in lung cancer patients. One study revealed that patients with lower SES reported more problems such as physical mobility, energy, role and physical functioning.[68] The other study showed that a higher level of education was significantly correlated with a decreased risk of lung cancer.[69]

These findings support the view that cancer patients with lower SES are more likely to report worse QoL than patients with higher SES.

Summary

From the above QoL reviews, the most commonly used quality of life instrument to compare cancer patients with non-cancer or general population is the Medical Outcomes Study 36-item Short Form Health Survey (SF-36).

The SF-36 is a generic HRQoL measure designed to examine a person's perceived health status over the past four weeks. It is a reliable well-validated questionnaire which has been used in a wide range of medical conditions.[70] The SF-36 consists of 36 items covering eight domains: physical functioning, role limitations because of physical health problems, bodily pain, general health, vitality, social functioning, role limitations because of emotional problems, and mental health.[71, 72] Then physical component summary scores (PCS) and mental component summary scores (MCS) are calculated to provide a global assessment of physical and mental functioning, respectively. Items are scored and all scores are transformed to a 0 to 100 scale. A higher score represents a better health status. In addition, the PCS and MCS have been standardized on norm-based scores (Mean = 50, Standard Deviation = 10) for the general U.S. population.

The SF-36 measures is less sensitive and responsive to the changes when assessing QoL of specific patient groups[18] and it is invaluable when comparing different diseases. However, it has strong practical advantages. Firstly, the SF-36 is a generic HRQoL measure, which can be applied to a wide range of diseases and health conditions including fatigue, physical and social activities, and not related to cancer. Secondly, it is applicable to many disease groups as well as the general population, and not limited to cancer. Therefore, it can be used to make comparisons between cancer patients and patients with other diseases as well as healthy populations.

In addition, the review of QoL literature revealed two key features regarding the health of cancer patients taking medications: a) cancer patients receiving medications experienced an impaired QoL compared with non-cancer patients; b) disparities such

as age, marriage, race/ethnicity, education, income, insurance and chronic conditions have been related to QoL in cancer patients.

2.3.2 Disparities on Prescription Medication Expenditures

One of the American Cancer Society's 2015 goals is eliminating disparities in the cancer burden of the U.S. population among different gender, race/ethnicity, residence, socioeconomic status (e.g., income, education, employment status, insurance status) groups.[4] The complex and interrelated causes of health disparities within each of these groups are likely due to different education, work, income, residence and overall standard of living levels.[4] Social barriers to high-quality cancer prevention, early detection and treatment services may also cause the disparities.[4] Unfortunately, the studies focusing on disparities on cancer medication expenditures are limited. For providing more adequate background related to this study, some literatures identified by Kholsa[73] and Lines[74] are also adopted in current study. This section will firstly introduce the effects of disparities on prescription medication expenditures based on identified studies. Then the studies focusing on out-of-pocket expenditures for cancer patients will be presented.

Effects of Age and Gender on Prescription Medication Expenditures

The actual relationship of cost to age and gender is not clear. When studying health utilization and expenditures, age and gender are the most common covariates used to adjust for patient characteristics when testing hypotheses about cost, because they are almost always available and are reasonable proxies for a person's need for service.[75]

Some studies show that more elderly patients (age 65 and older) than nonelderly patients incur prescription drug costs. Additionally, elderly patients incur more of the prescription medication expenditures, and pay more of these expenditures via out-of-pocket. Moreover, for elderly patients, their out-of-pocket proportion of total prescription expenditures is also larger.

The estimates from the year 1996 Medical Expenditure Panel Survey (MEPS) revealed that more of the elderly population incurred prescription expenses in comparison to the nonelderly (elderly 87% vs. nonelderly 62%), and elderly had more than twice as large average prescription expenses than nonelderly did ($825 vs. $321).[76] In addition, more of the elderly patients than nonelderly paid via out-of-pocket (52% vs. 41%).

Ezzati-Rice et al.[77] did a MEPS research based on year 2000 data and discovered that elderly people were much more likely than people under age 65 to have prescription medicine expenses (elderly 88.3% vs. nonelderly 58.5%), and their median prescription medicine expenses were about five times as high ($695 vs. $136).

One MEPS study by Xu[78] confirmed that the disparities of financial burdens still existed between elderly and nonelderly populations even after controlling for utilization or health care need. The results indicated that the elderly spent about three times as much of their incomes on out-of-pocket spending for prescription drugs as the nonelderly. They also had financial disadvantage in out-of-pocket proportion and income proportion. The comparisons of within-poverty-level revealed that with the low income level (125 - 199% of poverty) elderly were worse off than nonelderly in the same poverty class and in other income groups.

McKercher and his colleagues examined prescription drug use among elderly and nonelderly families based on year 1996 MEPS data.[79] They found that compared with nonelderly families, elderly families had greater prescription size, higher price and more drug use. Elderly families experienced almost twice increase in their out-of-pocket spending proportion of total expenditures (45.6% vs. 23.7%).

Likewise, some studies also analyzed the effect of gender on prescription medication expenditures.

Hodgson et al.[80] used various national survey data sources to estimate the year 1995 personal health care expenditures with regard to gender, age and diagnosis for

each type of health care service. This study indicated that male cancer patients paid less on prescription drugs than female patients (male $387 vs. female $597).

Ezzati-Rice et al.[77] found that females were more likely to incur prescription medicine expenses than males (female 69.2% vs. male 54.9%). The median expense per person was $219 for females and $146 for males.

In Medicare Chartbook 2010, one section analyzed Medicare and prescription drugs through Medicare current beneficiary survey cost and use files.[81] It indicated that the average per capita out-of-pocket spending by female Medicare beneficiaries was higher than that by male beneficiaries (female $4,490 vs. male $3,930).

Effects of Race and Ethnicity on Prescription Medication Expenditures

In health care, the differences of race and ethnicity are prevalent. According to Cancer Facts & Figures of American Cancer Society, compared with any other racial or ethnic group, African Americans have a higher probability to develop and die from cancer,[82] and Hispanics have lower incidence rates for either all cancers combined or for most common types of cancer when compared to whites.[83] Additionally, there is also a greater amount of uninsured or public insured among African Americans or Hispanics.[84] Furthermore, older minorities had lower overall health care utilization in contrast to non-Hispanic whites.[85] Thus the frequency of health care utilization including prescription medicine is lower among blacks and Hispanics, since they rely more on public coverage.

Ezzati-Rice et al.[77] used year 2000 MEPS data to analyze the healthcare expenses in the Unites States. It was found that minorities were less likely to incur prescription medicine expenses than whites/others. The percentages were 47.2% of Hispanics, 50.8% of blacks and 66.6% of whites/others. Whites/others ($214) incurred higher median prescription medicine expense per person with an expense than blacks ($125) and Hispanics ($92).

Winter et al.[86] pooled year 1996-2003 MEPS data to examine how race and health insurance impact on cardiovascular disease prescription medication use and

expense. It showed that the expenses for European Americans were significantly higher than those for African American, Hispanic Americans, or persons in the other racial group (mean $1,406 vs. $1,056, $1,169, $1,086 respectively; $p < 0.01$). Higher prescription medication expense was associated with being older, female, married, unemployed and living in the northeast. In addition, compared to participants with public or with dual public and private coverage, participants with private coverage spent less prescription medications (private coverage $1,194 vs. public coverage $1,931, dual public and private coverage $2,076, respectively; $p \leq 0.001$).

Tseng et al.[87] investigated insured diabetes adults' race/ethnicity in cost-related medication underuse. They found that African Americans and Latinos had higher cost-related medication underuse rates, lower income, lower education level and higher out-of-pocket drug costs than other races.

Effects of Socioeconomic Status (SES) on Prescription Medication Expenditures

Several researches showed that SES, including income, education, employment status and insurance status, was an important factor affecting prescription medication expenditures.

Using year 2001 MEPS data, Shin and Moon studied how prescription drug insurance related to prescription drug's use and spending.[88] The mean of total prescription drug expenditure for respondents with drug insurance ($1,032.2) was significantly lower in comparison to those without drug insurance ($1,293.2). Significant difference in out-of-pocket prescription drug spending was also found between respondents with drug insurance (46% of out-of-pocket spending for all health care use, 40% of prescription drug expenditure) and those without drug insurance (64% of out-of-pocket spending for all health care use, 69% of prescription drug expenditure).

Stagnitti[89] examined prescribed medicine expenditures in terms of sources of payment and insurance status by year 2003 data from MEPS. For those incurring a prescribed drug expense, the average prescription drug expense per Medicare beneficiary ($1,971) was almost three times as large as the average expense per

person in the non-Medicare population ($688). The average annual out-of-pocket prescription drug expense for Medicare beneficiaries was the highest for those people covered by Medicare only ($1,353) compared with those covered by Medicare and any private insurance ($892) or those covered by Medicare and public only insurance ($796). The uninsured had the lowest average annual total expense ($488) but the highest average annual out-of-pocket expense ($428) when compared with those with public insurance only (total expense $768 and out-of-pocket expense $226, respectively) and those with any private insurance (total expense $697 and out-of-pocket expense $271, respectively).

Ezzati-Rice et al.[77] indicated that the median prescription medicine expense per person was $174 for people living in metropolitan statistical area (MSA) and $239 for people not living in MSA in year 2000. People living in the West Region had the least probability to incur prescription medicine spending: 58.1% in the West versus 62.6% in the South, 64.1 % in the Midwest, and 64.3% in the Northeast. Those people also had the lowest median prescription medicine expenses: $135 in the West versus $172 in the Northeast, $204 in the Midwest, and $223 in the South. In addition, poor people had a lower likelihood of having prescription medicine expenses than high income people (poor 58.6% vs. high income 64.8%), and the median expense was less among poor people than for people with high income ($139 vs. $205).

Prescription Medication Expenditures and Quality of Life

The studies assessing prescription medication expenditures and patients' quality of life show that poor health status was associated with higher prescription expenditures.

Based on year 2000 MEPS data, Ezzati-Rice et al.[77] reported that people with better perceived health status were less likely to incur prescription medicine expenses in comparison to people in poor health. 49.0% of people with excellent perceived health had prescription medicine expenses. In contrast, 92.2% of people with poor perceived health had prescription medicine expenses.

A study demonstrated significantly worse health outcomes among middle-age and elderly Americans who reported restricted medications because of unaffordable cost.[90] Among the responders who reported good to excellent health at baseline, the percentage of those who had cost-related medication restrictions reported a significant decline in their health status was higher than that of those who had not (32.1% vs. 21.2%; adjusted odds ratio 1.76). Cardiovascular disease has the strongest association with cost-related medication restriction than diabetes, arthritis and depression.

Harman et al.[91] used year 1999 MEPS data to indicate that older Americans with depression have relatively high out-of-pocket expenditures. Mean out-of-pocket expenditures for elderly Americans with depression were $1,835 in 1999. Most of the spending ($1,090) was on prescription drugs. Patients with depression had greater mean out-of-pocket spending than those with hypertension and arthritis.

Farmer and Ferraro examined the interactive relationship between race and SES on health for Americans with a 20-year period.[92] This study indicated that blacks reported more serious illnesses and poorer self-rated health than whites when starting the study, and this disparity last 20 years. It was also found that race and education had significant associations with health outcomes: at the higher levels of SES, the racial disparity in self-rated health was the largest; blacks did not have the same improvement in self-rated health as whites did when education level increased.

Lee and Skrepnek[93] used year 2006 MEPS data to examine the associations of out-of-pocket health care expenditure and quality-of-life (QoL) with physical activity in patients with hypertension. This study showed that patients had an average of $1,453 ± 47 out-of-pocket health care expenses. Average physical and mental QoL scores were 42.4 ± 0.2 and 50.2 ± 0.1 respectively. In addition, physical inactivity was associated with 14.9% ± 5.2% greater out-of-pocket health care expenses, 7.4% ± 0.8% lower physical QoL, and 3.3% ± 0.7% lower mental QoL (all $p < 0.0001$).

A study used population-based survey to examine the determining factors of out-of-pocket health expenditure in China. This study indicated that highest out-of-pocket health expenditure incurred among the persons who had perceived quite serious illness and self-reported poor health status.[94]

Out-of-Pocket Expenditures of Cancer Patients

There are seven studies assessing cancer patients' out-of-pocket expenditures in the U.S. Six studies conducted national estimates of medical costs by national survey data, which focusing on nonelderly, elderly cancer patients or cancer survivors. One study examined expenditures of breast cancer patients.

Hodgson et al.[80] used various national survey data sources to estimate the year 1995 personal health care expenditures. They found that male cancer patients paid less prescription drugs than female patients. Female cancer patients had an average of $567 on prescription drugs in year 1995, while the number for male cancer patients was $387. Elderly cancer patients had an average of $19,212 in year 1995 on expenditures ($366 for prescription drugs) while non-elderly counterparts had an average expenditure of approximately $21,964 ($588 for prescription drugs).

Howard et al.[95] compared year 1996-1999 data from MEPS with year 1999 data from Marketscan database, which collects claims data from commercial, Medicare supplement and Medicaid populations. The total cancer treatment-related spending by nonelderly cancer patients was $20.1 billion in MEPS database (6.5% was spent via out-of-pocket expenditures), and $17.2 billion in Marketscan database (4.1% was spent via out-of-pocket expenditures).

One study used the same year 1996-1999 MEPS data to examine health insurance and spending among nonelderly cancer patients.[96] This study revealed the uninsured patients spent less of the health care spending ($3,606) compared with Medicare ($6,080), Medicaid ($5,943) and privately insured patients ($6,550). Additionally, uninsured patients paid more out-of-pocket than insured patients paid.

Using year 1996-2003 data from MEPS, Banthin et al.[97] reported that individuals aged 55 to 64 years, with poor and low-income, without group coverage, living in a non-city area, in fair or poor health, having any type of limitation, or experiencing a chronic medical condition had higher-than-average risk of incurring high total burdens.

Langa et al.[98] did national estimates of elderly patients by using data from the year 1995 Asset and Health Dynamics Study, which is a nationally representative survey of non-institutionalized elderly population in the U.S. They found that prescription medications ($1,120 per year) accounted for most of the additional out-of-pocket expenditures associated with cancer treatment. Low-income cancer patients undergoing treatment spent about 27% of their yearly income on out-of-pocket expenditures; in contrast, high-income individuals with no history of cancer spent only 5%. Elderly cancer patients spent additional $670 (48% were attributed to prescription medication expenditures) per year on current cancer treatments, despite adjusting for contributing factors, such as demographic characteristics, socioeconomic status.

Another study used MEPS data from year 2001 to 2007 to estimate of medical expenditures for adult cancer survivors aged less than 65.[99] It indicated that cancer increased the risk of high out-of-pocket expenditures. The mean annual expenditures on all services were higher for survivors who were newly diagnosed ($16,910) than long term survivors ($7,992) and other adults ($3,303).

Arozullah et al.[100] examined the financial burden of insured breast cancer patients. In all, 156 patients received most or all cancer care at an academic hospital between October 1999 and November 2002 were interviewed by a questionnaire. The mean total out-of-pocket costs averaged $1,455 per month, of which about half was lost income ($727), 41% was for non-reimbursed direct medical costs ($597), and 9% for direct nonmedical costs ($131). The most commonly reported out-of-pocket expenditures were for medications (80%). The financial burden of breast cancer patients was 98% for those with annual household incomes less than $30,000, 41% for those with annual household incomes between $30,001 and $60,000, and 26% for those with annual household incomes more than $60,000, respectively.

Summary

The studies examining expenditures associated with cancer disparities are limited; particularly the studies referring to cancer prescription medication expenditures are

scare. Yet the identified studies have shown that more elderly patients than nonelderly patients incur prescription drug costs and incur more of the prescription medication expenditures. Female patients pay more on prescription drugs than male patients. Compared with whites, more racial and ethnic minorities were covered by public health insurance and they spent lower out-of-pocket expenditures for health care including prescription expenditures. Furthermore, individuals with lower SES or poorer health status incur higher health expenditures.

Identifying the characteristics of patients who are probable to spend large amounts of out-of-pocket medication expenditures, as well as those services that are most likely to generate such expenditures is important. To summarize from the points above, out-of-pocket spending varies by age (especially the elderly), gender (especially female), income (especially low-income), insurance status (especially uninsured), chronic conditions, and the self-reported health status (especially poor health status).

2.4 Methodology

This study is a cross-sectional analysis on health-related quality of life and expenditures of cancer patients with prescription medications. For better documenting the disparities affecting HRQol and cancer prescription medication expenditures, beyond the data analysis methods introduced by MEPS, some other methods in the studies of Xie et al.[101] and Sung[102] are considered as references as well. In this section, the data source used is described firstly, and then the data files chosen to meet the study's goals will be introduced. After that, the study sample, variables and statistical analytic methods will be presented.

2.4.1 Data Source

The data from this study were collected from the Medical Expenditure Panel Survey (MEPS), which is administered by the Agency for Healthcare Research and Quality (AHRQ) under the U.S. Department of Health and Human Services (HHS) (http://www.meps.ahrq.gov/mepsweb). The MEPS is a set of large-scale surveys

designed for individuals and families, their medical providers (e.g., doctors, hospitals, and pharmacies) and employers across the United States.[42] The primary care practice-based research networks are supported by AHRQ link information on health services with patient-reported outcomes data in community-based clinical care settings for more than 38,000,000 patients in 49 states.[103] It provides nationally representative estimates on the utilization, insurance coverage, expenditures, and payment sources of health care for the U.S. civilian non-institutionalized population.

The core component data in the MEPS is the Household Component (HC) data. This data is based on questionnaires for individual household members and their medical providers.[42] It contains the information of respondents' health status, demographic and socioeconomic characteristics, employment status, access to health care, satisfaction with health care and prescribed medication information. In addition, since year 2000, HC has included a Self-Administered Questionnaire (SAQ) that contains HRQoL measures for adults aged over 18 years. The overall response rate for this questionnaire is 92.7% in 2008.[104]

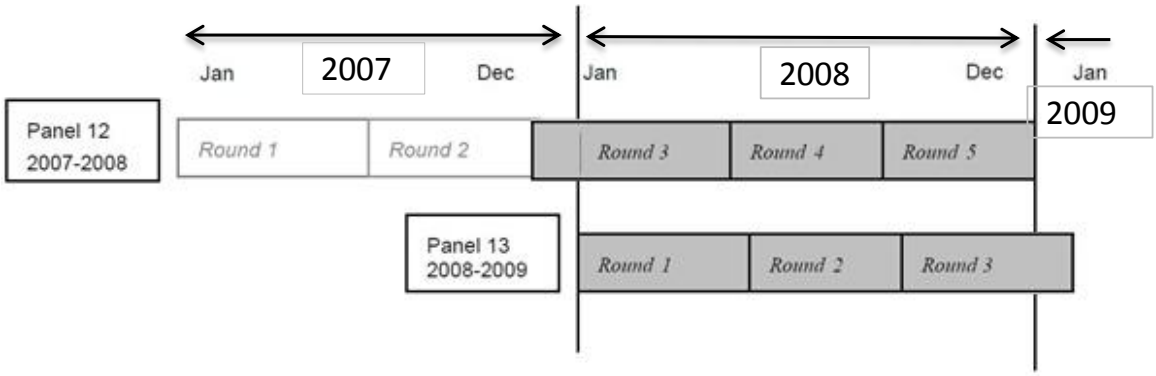
The sampling frame for the MEPS Household Component is randomly drawn from individuals who have responded to the previous year's National Health Interview Survey (NHIS). The NHIS follows a complex multi-stage probability design which samples in three stages: the first stage of sample selection is an area sample of Primary Sampling Units (PSUs), which consist of counties; in the second stage, blocks are selected; and in final stage, households are sampled.[104] In each selected family, all civilians are key, in-scope and are surveyed. A key, in-scope person means that the person responded to MEPS for the full period of time (in this study, it is year 2008).[104]

The MEPS Household Component has an overlapping panel design. Each panel is interviewed totally five times covering two full calendar years.[105] Every year a new MEPS panel that includes a nationally representative sample of households is introduced into the survey. Interviews last an average time of 90 minutes and are conducted with computer-assisted personal method. The first interview contains many detailed questions (e.g., respondents' health status, income, employment status, eligibility for Medicare, Medicaid or private insurance coverage, use of health care

services, payment for care, etc.). The subsequent interviews ask about the changes since the last interview, such as what employment status has changed, what medical care has occurred. In supplemental modules, relevant questions (e.g., access to health care, health status) are asked periodically.[105] This design could help to determine how these changes are related.

The data used in this study pertain to calendar year 2008. They were collected in Rounds 1, 2, and 3 for MEPS Panel 13 and Rounds 3, 4, and 5 for MEPS Panel 12. Round 3 for a MEPS panel is designed to overlap two calendar years, as illustrated in Figure 4.

Figure 4: Illustration of Panels and the Round Series in MEPS Survey Year 2008



Adapted from: 2008 Full Year Consolidated Data File, Agency for Healthcare Research and Quality.[104] Page 109.

This public use dataset contains 33,066 persons who participated in the MEPS Household Component in 2008.[104] These persons were part of one of the two MEPS panels for whom data were collected in 2008: Rounds 4 and 5, and part of Round 3 of Panel 12 or Rounds 1and 2, and part of Round 3 of Panel 13.

For examining patients' HRQoL and prescription medication expenditures, the following three data sources are selected from 2008 household component files:

- MEPS HC-118A: 2008 Prescribed Medicines File
- MEPS HC-120: 2008 Medical Conditions File
- MEPS HC-121: 2008 Full Year Consolidated Data File

The 2008 Prescribed Medicines public use data set (MEPS HC-118A) contains detailed prescription medicines information obtained from pharmacy providers that household sampled persons frequented. On this file, each record includes the following information: an identifier for each prescribed medicine; detailed medicine characteristics (e.g., national drug code (NDC), medicine name, quantity of the medication dispensed, form of the medications, unit of measure, and dosage strength); conditions associated with the medicine; the first date that the person start to use the medicine; total expenditure; payment sources; contact information of pharmacies that filled the prescriptions.[106] To use this file for cancer patients, a list of reported use of prescription medications associated by all household with a primary diagnosis corresponding to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of "140-239" was complied. The detailed ICD-9-CM codes for cancer in this study are listed in Appendix 1.

The MEPS HC-120, Medical Conditions File contains verified information about respondents' medical conditions. These conditions are transformed to fully-specified ICD-9-CM codes by professional coders based on the verbatim text recorded by the interviewers.[107] All the codes were verified, and error rates were less than 2.5% for any coder.[108] From these data, patients with cancer (ICD-9-CM codes from 140 to 239) were first identified, and then comorbid conditions were identified for each person.

The MEPS HC-121, 2008 Full Year Consolidated Data File contains variables related to participants' demographics, income and tax filing, person-level condition, health status, disability days, access to care and quality of care, employment status, health insurance, patient satisfaction, and person-level medical care use, expenditures, and sources of payment.[104] All patients' variables and health related information are extracted from this file. Demographic and socioeconomic status variables include age, gender, race/ethnicity, region, marital status, education attainment, personal total income and family poverty level. Metropolitan Statistical Area (MSA) status is also used as a geographic variation. With regard to health insurance status, this study used the summarized health insurance coverage indicators for the respondents in 2008: Medicare, Medicaid, other public insurance, private insurance and being uninsured. In

addition, patient-reported health status information was collected through Self-Administered Questionnaire (SAQ) in this data file.

Reasons for Using MEPS

In the United States, there are many national survey databases conducted by the U.S. Department of Health & Human Services (HHS), such as MEPS, National Ambulatory Medical Care Survey (NAMCS), Healthcare Cost and Utilization Project (HCUP) etc.

The first reason for choosing MEPS data files for this research is that MEPS is a nationally representative survey data with high accuracy and reliability. Detailed information on prevalence and incidence along with comorbidities, medication, health utilization, medical services received, expenditures could be obtained from MEPS. In addition, there was a high percentage correlation between patient and provider-reported diagnoses.[109, 110]

The second reason is that MEPS allows researchers to identify the disease by ICD-9-CM codes instead from the answers to the questions. At first, the diagnoses of cancer were based on the verbatim text of each patient's self-reported medical condition. Subsequently, a professional coder assigned fully-specified ICD-9-CM codes to that verbatim text. Additionally, each code for self-reported medical condition was verified by medical providers and pharmacies that the respondents frequented. The error rate did not exceed 2.5% for any coder.[108] Fully-specified ICD-9-CM codes were in three-digit form in order to protect the confidentiality of respondents. [108]

The third reason is the reliability of drug use information. In order to avoid respondent underreporting prescription data, the MEPS relieves the household of the report burden by obtaining the computerized printouts from respondents' pharmacy providers that the respondents identified as their source of care under patients' permission.[111] The computerized printouts contains detailed financial information on every prescription purchase, such as the date the drug dispensed or refilled, the NDC, the drug name including generic and/or brand name, the strength of the drug, the quantity of the drug dispensed, total charge, payment sources and the amount of

payment made by each source.[111] When computerized printouts are unavailable from a pharmacy provider, the survey staff attempt to secure written data forms when possible. The information collected from pharmacy providers has to be imputed or match to all the household drug mentions for public release of the household prescription data.[111]

The fourth reason is that MEPS collects data on specific health care services and captures all related costs, not just single payer costs. The data allows for basic descriptive statistics and behavioral analyses of the U.S. health care system, including detailed demographic, health status, behavior, and socioeconomic status information; conditions and diseases direction; utilization of health services, expenditures of health care, and payment sources for health care.[105] It also support exporting the impact of health status on health care use, expenditures, choice of health insurance and household decision making.[105]

The final reason is that the data files released by MEPS are easy to access. There is no permission required for access to all public use data files, which are also freely downloadable. All public use files are sorted according to data year. In addition to the raw data, each data file includes a document file containing detailed technical and programming information (e.g., how the data were collected, how the variables were edited), survey sampling information and variable-source crosswalk; a codebook containing alphabetical and positional listing of variables, and unweighted and weighted frequencies; statistical program (SAS or SPSS) statements and programming examples; and the contents of questionnaires used in interviewing MEPS respondents.[42]

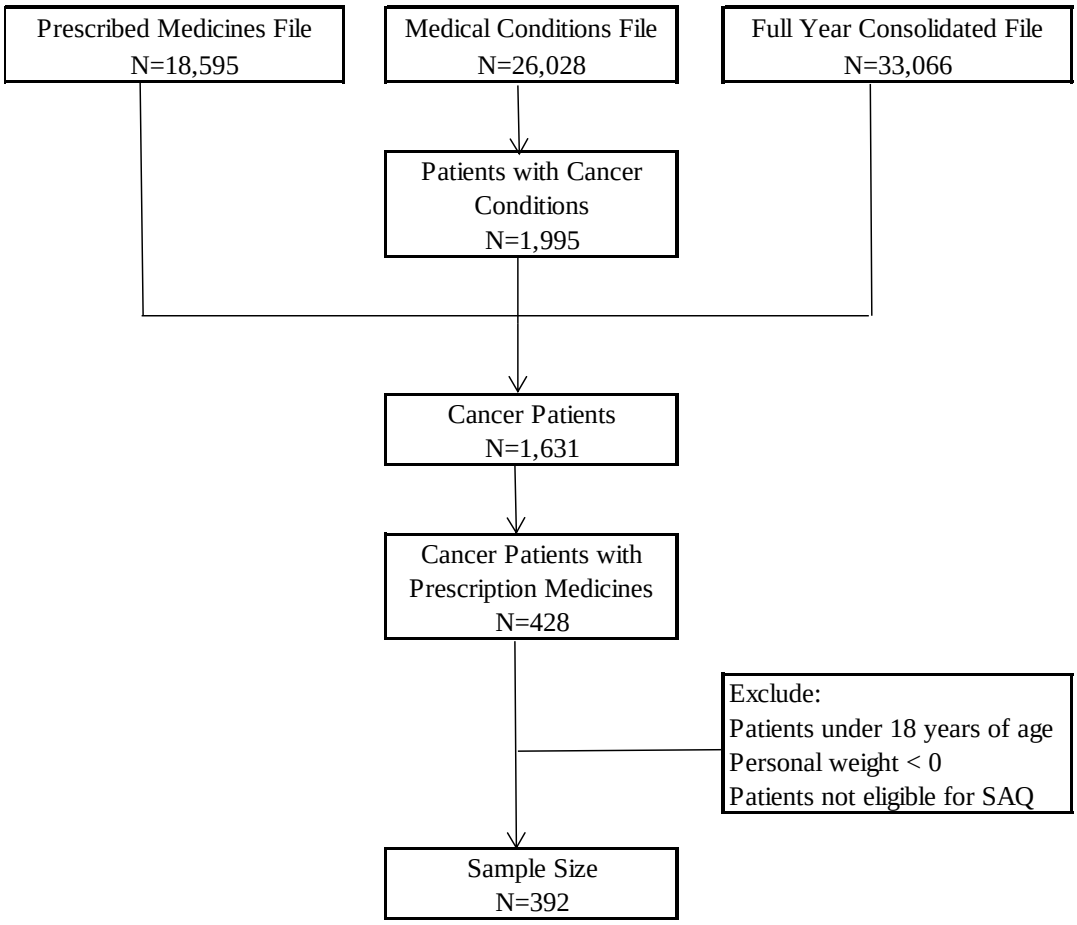
2.4.2 Definitions of Study Sample and Variables

This section will firstly introduce how the study sample is selected. Then a brief explanation about the dependent and independent variables will be presented, respectively.

2.4.2.1 Study Sample

Individuals were identified for inclusion in this study if they reported diagnosis of cancer (ICD-9-CM codes from 140 to 239). In addition, only individuals who were at least 18 years old and had positive personal weight were included. The reason for extracting patients with positive personal weight is that the current study only included in-scope persons who responded to MEPS during the full 2008 year. The detailed explained will be found in the next section - "statistical analytic methods". Moreover, patients who did not have Self-Administered Questionnaire (SAQ) data were excluded, because only SAQ had HRQoL information. The selection process of the study sample is illustrated in Figure 5.

Figure 5: Flow Chart of the Study Sample Selection



In 2008, 33,066 persons participated in the Household Component of the MEPS. There were 1,631 persons reported that they were diagnosed with cancer. 31,435 persons were without cancer diagnosis. Among these cancer patients, only 428 (26%) patients were treated with prescription cancer medications during the full year of 2008. After excluding patients who were less than 18 years of old, with negative personal weight and not eligible for SAQ, the final sample included 392 cancer patients with prescriptions. Patients without cancer diagnosis were age-matched to cancer patients with prescription medications at 1:5 ratios. Hence, 1,960 age-matched persons without cancer diagnosis were identified from total population.

2.4.2.2 Dependent Variables

1) Patient-reported Outcomes from SAQ

The Self-Administered Questionnaire (SAQ) is a paper-and-pencil questionnaire. It is designed to collect a variety of health status and health care quality measures of adults. MEPS interviewers distribute hard copies of the SAQ to members of sampled households. Then completed SAQs are returned by mail. The pooled response rate of SAQ for the year 2008 is 92.7 %.[104] The SAQ includes three Health-related Quality of Life (HRQoL) instruments: the Medical Outcomes Study 12-item Short Form Health Survey, Version 2 (SF-12v2) for measuring overall health status, the Kessler Index (K-6) for measuring non-specific psychological distress, and the Patient Health Questionnaire (PHQ-2) for measuring depression.

a. Short-Form 12 Version 2 (SF-12v2)

The Medical Outcomes Study 12-item Short-Form Health Survey (SF-12) is a generic HRQoL measure with items derived from the 36-item Short Form Health Survey (SF-36). It is a brief and easy (usually takes two to three minutes to complete) HRQoL measure of overall health status.[112, 113]

SF-12 includes twelve questions covering the following eight multi-item subscales:

- physical functioning (2 questions);
- role limitations because of physical health problems (2 questions);
- bodily pain (1 question);
- general health perceptions (1 question);
- vitality (energy/fatigue) (1 question);
- social functioning (1 question);
- role limitations because of emotional problems (2 questions);
- general mental health (2 questions: psychological distress and psychological well-being)

The two questions of physical functioning are scored from 1 to 3, higher score indicates less limitations. The other questions are scored from 1 to 5, higher score indicates better health. But for general health perceptions and bodily pain, higher score indicates poor general health and aggravating pain.

Then, physical and mental summary scales (Physical Component Summary [PCS-12] and Mental Component Summary [MCS-12]) from all twelve questions are generated by a scoring system. PCS-12 weighs more heavily on the response to the first four subscales, while MCS-12 weighs more heavily on the response to the last four subscales. Both summary scales are transformed to a scale of 0 (worst health) to 100 (best health) by means of norm-based scoring. Higher scores represent better physical or emotional function. Norm-based PCS-12 and MSC-12 scores for the U.S. general population were scaled with a mean of 50 and standard deviation of 10. That is, a score of more or less than 50 indicated that physical / emotional health was better or worse, respectively, than the general U.S. average. Item level of SF-12 responses, PCS-12 scores and MCS-12 scores are available for adult respondents in the MEPS data files. In year 2001 and 2002, the SF-12 Version 1 was administered; starting in year 2003, the SF-12 Version 2 replaced Version 1. Compared with version 1, version 2 improved a lot, such as increasing the precision of the eight health profiles, decreasing ambiguity in the phrasing of some questions, and providing normative comparisons.[114] The evaluation of adequate validity and reliability of the SF-12v2 in the MEPS can be found in the publication by Cheak-Zamora et al[115], which supports

the use of the SF-12v2 to evaluate the health status of the population and changes in health status over time.

b. Kessler Index (K-6)

The Kessler Index (K-6) was developed by Kessler and colleagues to measure non-specific, rather than disorder-specific psychological distress.[116] The six-item questions assess a person's non-specific psychological distress during the past 30 days. Persons are asked to rate how often they felt

- nervous;
- hopeless;
- restless or fidgety;
- so sad that nothing could cheer you up;
- that everything was an effort;
- worthless;

Each question uses the values 0 (none of the time), 1 (a little of the time), 2 (some of the time), 3 (most of the time) and 4 (all of the time). A summation of the six variables above provides an index score ranging from 0 to 24. Higher value of K-6 index score indicates a greater tendency towards serious mental disability. K-6 summary score ≥ 13 is the optimal cut point for the prevalence of serious mental illness in the national population.[117]

c. Patient Health Questionnaire (PHQ-2)

The PHQ-2 is made up of two items to assess the frequency of the person's depressed mood and decreased interest in usual activities.[118] The two items are "Over the last two weeks, how often have you been bothered by 1) little interest or pleasure in doing things 2) feeling down, depressed, or hopeless?" For each item, the response scores are 0 (not at all), 1 (several days), 2 (more than half the days) and 3 (nearly every day), respectively. There is also a summation of the values of the two variables above ranging from 0 through 6. A higher score indicates more serious depression. The authors suggest a score of 3 as the optimal cut-point for screening purposes.

2) Prescription Medication Total and Out-of-Pocket Expenditure

In the MEPS Prescribed Medicines File, expenditures refer to actual money paid for prescribed medications. More specifically, expenditures defined as the sum of payments for health care received, including out-of-pocket payments and payments made by each source such as private insurance, Medicaid, Medicare and other sources.[106] Expenditures for over-the-counter medications are not included. Such definition in MEPS represents improvements over the predecessors of MEPS (i.e., the year 1987 National Medical Expenditure Survey and the year 1977 National Medical Care Expenditure Survey), which included information on *charges* rather than *sum of payments* to measure expenditures.[106] The reason of adopting this change is that the increasingly common practice of discounting charges causes charges gradually becoming an improper proxy for medical expenditures during the 1990s.[106]

Total Expenditure

The total expenditure is calculated from major twelve sources of payments categories. On page 15 of "MEPS HC-118A: 2008 Prescribed Medicines" document downloaded from the website of Agency for Healthcare Research and Quality, these categories are introduced as follows:"

- Out-of-pocket by user (self) or family;
- Medicare;
- Medicaid;
- Private Insurance;
- Veterans Administration (VA) / Civilian Health and Medical Program of the Department of Veterans Affairs (CHAMPVA), excluding TRICARE (military health services);
- TRICARE;
- Other Federal sources, includes Indian Health Service, Military Treatment Facilities, and other care by the Federal government;
- Other State and Local Source, includes community and neighborhood clinics, State and local health departments, and State programs other than Medicaid;

- Worker's Compensation;
- Other Unclassified Sources, includes sources such as automobile, homeowner's and liability insurances, and other miscellaneous or unknown sources;
- Other Private, any type of private insurance payments reported for persons not reported to have any private health insurance coverage during the year as defined in MEPS; and
- Other Public, Medicaid/Medicaid payments reported for persons who were not reported to be enrolled in the Medicaid/Medicaid program at any time during the year. "[106]

The last two are additional sources of payment variables (other private and other public). They were created to sort apparently inconsistent payments between insurance coverage and payment sources.[106]

Out-of-Pocket Expenditure

In the MEPS Prescribed Medicines File, out-of-pocket expenditures are the prescribed medication spending paid by user or family.[106] They also include cash payments for coinsurance and deductibles, services, supplies and other items not covered by health insurance, but the premiums of health insurance, whether directly paid or withheld by employers, were excluded in this study.[119]

It is important to note that the total number of prescription medications in MEPS data is not differentiated. That is, all refills are included.

2.4.2.3 Independent Variables

In order to make the outcomes more explainable and understandable, this study modified a few variables and regrouped some values. All the independent variables still have the same names as those in the MEPS survey. Totally, there are five categories of independent variables: demographic variables (i.e., age, gender, race, ethnicity, marital status, and geographic variation), socioeconomic status (i.e.,

education attainment, income, health insurance coverage, and prescription insurance status), currently smoke, chronic conditions and proxy report.

1) Demographic Variables

Age

Age was calculated from the date of birth and indicated age status as of 12/31/2008. In order to analyze the differences between age groups, dummies were used to account for different age categories: 18-39 years, 40-64 years, and above 65 years. 65 years and older category was the reference group.

Gender

Gender was classified in to male and female. Male was the study reference group.

Race

The race questions in the MEPS have been revised starting in year 2002. In the 2008 survey, races included: 1. White; 2. black; 3. American Indian/Alaska Native; 4. Asian; 5. Native Hawaiian/Pacific Islander; 6. multiple race.[104] This study recoded the race into three groups: white, black and other. White population was the study reference group.

Ethnicity

Ethnicity included Hispanic and non-Hispanic, in which the latter was the study reference group.

Marital Status

The MEPS interview had six categories to measure marital status in questionnaire: 1. Married; 2. Widowed; 3. Divorces; 4. Separated; 5. Never married; 6. Under 16 - inapplicable.[104] Individuals under 16 years old were considered as inapplicable data.

This study only extracted individuals who were older than the age of 18. A dummy was used to regroup marital status. The new code 1 was for married and 0 was for unmarried. Here, unmarried was the reference group.

Geographic Variation - Census Region

Census region was collected for the main four areas of the U.S.: Northeast, Midwest, South, and West. West was the reference group. The states for each region will be introduced in Appendix 2.

Geographic Variation - Metropolitan Statistical Area (MSA)

The code of the MSA was 1 and non-MSA was 0, in which the latter was the reference group.

2) Socioeconomic Status (SES)

Education Attainment

In 2008 survey, the number of years of completed education and the highest degree of education indicated personal education level.[104] This study created four new levels according to the total years of education completed: 1. Less than 8 years; 2. High school diploma (including school grades from 9 to 12); 3. Some college (including college year from 1 to 3); 4. Bachelor's degree and other higher degrees. The last group was the reference group.

Income – Total Person-level Income

The definitions of income and poverty categories used to construct the related variables in this file were taken from the 2008 poverty statistics developed by the Current Population Survey (CPS).[104] Income variables included total person-level income and family income. Total person-level income was the sum of all income components with the exception of a person's tax refunds and capital gains.[104] In this study, it was divided into low (< $15,000), middle (between $15,000 and $20,000)

and high categories (> $20,000). High person-level income category was the reference group. Family income was related to poverty status as follows.

Income - Poverty Status

Page 30 of "MEPS HC-121: 2008 Full Year Consolidated Data File" defined family income as follows: "family income was derived by constructing person-level total income comprising annual earnings from wages, salaries, bonuses, tips, commissions; business and farm gains and losses; unemployment and workers' compensation; interest and dividends; alimony, child support, and other private cash transfers; private pensions, Individual Retirement Account (IRA) withdrawals, social security, and veterans payments; supplemental security income and cash welfare payments from public assistance, Temporary Assistance for Needy Families, and related programs; gains or losses from estates, trusts, partnerships, S corporations, rent, and royalties; and a small amount of "other" income."[104] Person-level incomes were summed over family members to yield the family-level total income. Then, family-income was divided by the applicable poverty line (i.e., based on family size and composition) and categorized as a percentage of the poverty line.[104] The five categories were as follows: 1. negative or poor (i.e., less than 100%); 2. near poor (i.e., 100% to less than 125%); 3. low income (i.e., 125% to less than 200%); 4. middle income (i.e., 200% to less than 400%); 5. high income (i.e., greater than or equal to 400%).[104] However, since less than 5% of the study sample were classified as near poor, the lowest two categories were combined. High family income group was the reference group.

Health Insurance Coverage

In this study, health insurance coverage was re-categorized as Medicare, Medicaid, other public insurance, private insurance and uninsured. Each variable was binary coded. Value 1 indicated that the person was covered for at least one day of one month during year 2008; value 0 indicated that the person was not covered for a given type of insurance for all of year 2008. Patients covered by private insurance were the reference group.

Prescription Insurance Status

This study focused on the patients with cancer prescription medications; therefore prescription insurance was also an important independent variable. Patients not covered by prescription insurance were the reference group.

3) Currently Smoke

According to the data from the American Cancer Society's Cancer Prevention Study II, the smoking-related cancer deaths continue to rise.[4] Smoking accounts for at least 30% of all cancer deaths and 87% of lung cancer deaths.[4] Hence, smoking was also considered as an independent variable. Former smokers were the reference group.

4) Chronic Conditions

The chronic conditions: heart conditions (including hypertension, coronary heart disease, angina, and heart attack), high cholesterol, diabetes, joint pain, arthritis, asthma etc. were identified. A dummy was used. The reference group included those who did not have the condition of interest listed above. For example, for the group of patients experiencing heart conditions, the reference group is those who did not experience heart conditions.

5) Self-Report

The code of the self-report was 1 and proxy-report was 0, in which the latter was the reference group.

Independent Variables of Measuring Lost Productivity

Here, the independent variables of measuring lost productivity are presented as well, because as part of indirect cost, a simple descriptive analysis will be conducted. Lost productivity due to cancer prescriptions was measured by:

- whether the individual had a job in the past year (yes/no),
- whether the individual had limitations to work in the past year due to health problems (yes/no),
- number of days lost from work in the past year due to health problems,
- number of days spent in bed in the past year due to health problems.

2.4.3 Statistical Analytic Methods

The MEPS data is a complex survey design that used cluster and stratified sampling. Hence, all respondents in the database were assigned person-level weights to enable calculation of national estimates. In the database "MEPS HC-121: 2008 Full Year Consolidated Data File", weight variables are provided to convert sample statistics to population parameter. Each record for each key, in-scope person was assigned with a single full year person-level weight (in year 2008, this variable is PERWT08F). A key person either was a member of a National Health Interview Survey (NHIS) household when doing the NHIS interview, or became a member of a household after being out-of-scope at the time of the NHIS interview (e.g., newborns, persons returning from military service, or living outside the United States).[104] A person is in-scope means that he or she is a member of the portion of the U.S. civilian non-institutionalized population at any time.[104] A single person-level weight variable (SAQWT08F) has been provided for use the data obtained from the SAQ.

The sample population represented in the current study had to be classified as a key, in-scope person who responded to MEPS for the full year of 2008, which means that the person should have a positive person-level weight in 2008 full-year (PERWT08F > 0).

In addition, the clustered nature of data that include both individual-level and area-level covariates requires that researchers use models to adjust the standard errors for the structure of the data. Several methodologies, including the Taylor-series linearization method, have been developed to deal with this problem. Various software packages permit analysts to implement these methodologies, such as SAS (version 8.2 and higher), Stata, SPSS (version 12.0 and higher), and SUDAAN. When

using these methods, sampling strata and Primary Sampling Units (PSUs) must be specified for the variance estimation. On MEPS data file, the variables VARSTR (Variance Estimation Stratum) and VARPSU (Variance Estimation PSU) are provided for the use in the variance estimation programs.[104]

This study used SAS software version 9.2 (SAS Institute, Cary, NC) for statistical analysis. Due to the complex sample design of MEPS, PROC SURVEYFREQ, PROC SURVEYMEANS and PROC SURVEYREG procedures in SAS 9.2 which incorporated survey weights were used to calculate sampling errors of estimates. 5% level was used as cutoff for statistical significance.

Univariate Analysis

Patient characteristics of cancer and age-matched non-cancer population, including demographics, insurance coverage and chronic conditions, were described. Weighted population estimates, mean HRQoL scores, mean expenditures of total and out-of-pocket, were tabulated using the survey weights. As part of indirect cost, a simple descriptive analysis was conducted about lost productivity. Descriptive statistics between key variables were computed based on frequencies and percentages for categorical variables, and mean and standard deviation for continuous variables.

Bivariate Analysis

To assess the differences of patient characteristics between cancer and age-matched non-cancer population, categorical variables were compared using Chi-square test, while continuous variables were compared using T-test. Responses to the quality of life questions for the two groups were compared using the Pearson correlation coefficient.

Multivariate Analysis

How certain patient characteristics strongly associated with HRQoL and high total/out-of-pocket prescription medication expenditures were examined by multivariate regression analyses, respectively.

1) Health-related Quality of Life (HRQoL)

To control for potential confounders, multivariate ordinary least squares (OLS) regressions were conducted to further investigate the differences in these HRQoL measures between cancer and non-cancer populations. The rationale for using OLS regression was that dichotomizing the QoL responses may cause information loss, variance reduction, and power loss.[120] In addition, the QoL responses were normally distributed, which permitted the use of OLS regression. The multivariate analysis was controlled for patient characteristics (age, gender, race, ethnicity, marital status, region, education, personal-level income and poverty level), prescription insurance status, currently smoke, chronic conditions and proxy reporting.

The regression model is:

$$HRQoL = \alpha + \beta_1 (age) + \beta_2 (education) + \ldots \beta_n (proxy\ reporting)$$

Where α is an intercept constant, and β is a non-standardized multiple regression coefficient to be estimated. The term HRQoL was a continuous dependent variable, which was measured as PCS-12, MCS-12, K-6 and PHQ-2.

The weighted model was constructed by the SAS SURVEYREG procedure, which was developed to perform regression analysis for complex survey sample designs, including unequal weighting.[121] Therefore, incorporating the sampling weights in the weighted model was enabled.

2) Total and Out-of-Pocket Prescription Medication Expenditures

To assess the factors affecting medication expenditures associated with cancer and estimate the predicted expenditures, least-squares regression was used. The factors included patients' demographics, socioeconomic status (SES), chronic conditions and HRQoL scores. The regression was weighted, and the standard errors were adjusted for the survey design.

Logarithmic Transformation of Expenditures

Because expenditure data in MEPS were found to be highly skewed, a logarithmic transformation of total/out-of-pocket prescription medication expenditures was used as the dependent variable.[75] The logarithm of the expenditure variable can be presented by "log (prescription medication expenditures + 1)". When calculating a logarithm for individuals with zero expenditure, one dollar was added to expenditures.

Exponentiated Regression Coefficients, $(e^{\beta} - 1) \times 100$

The exponentiated regression coefficients, which provide the estimated ratios of expenditures, were used to explain the outcomes of logarithm scale of expenditures. "exponentiated regression coefficients $(e^{\beta} - 1) \times 100$" can be used to interpret logarithm scale of expenditures. For example, the expenditures in the group of population with high blood pressure were how much percentage higher or lower than that in the reference group without high blood pressure.

Retransformations

In order to calculate the cost in economic analysis, the transformed results must be retransformed back to the original scale. For producing unbiased estimates of the mean expenditures, adjusted mean expenditures were calculated by exponentiating the least-squares means, and then multiplying the result by a "smearing" coefficient, which was the sum of the exponentiated residuals divided by the sample size.[122]

The regression model is:

$$\text{Expenditure} = \alpha + \beta_1 (\text{age}) + \beta_2 (\text{insurance coverage}) + \ldots \beta_n (\text{SF-12 score})$$

2.5 Study Results

In this section, results of describing and comparing the characteristics of cancer

population with prescription medications and age-matched non-cancer population are presented firstly. Secondly, the HRQoL outcomes between these two groups are provided, including the factors affecting HRQoL of cancer population with prescription medications. Thirdly, the mean distributions of total and out-of-pocket prescription drug expenditures of cancer patients by characteristics, and the results of multivariate analyses are presented.

2.5.1 Descriptive Statistics

Table 6 describes the proportions for the individual characteristics of the population obtained by incorporating primary sampling units, strata and person weights. Patients without cancer diagnosis were age-matched to cancer patients with prescription medications at 1:5 ratios. The final sample, 392 cancer patients with prescription medications were derived from the 2008 MEPS with age of 18 and above, while 1,960 patients were without cancer diagnosed.

As shown in the table, the mean age for both groups was 62.7 years old. Most patients were aged 40 and above. Individuals with cancer were disproportionately more female. Both groups were predominately white and Non-Hispanic. The majority of individuals in both groups were currently married and living in MSA. Cancer participants had more years of education (13.2 years for cancer patients vs. 12.6 years for non-cancer patients; $p < 0.0001$) and greater percentage of high family income (45.4% for cancer patients vs. 38.7% for non-cancer patients; $p = 0.0318$) than participants without cancer. With regard to insurance, more cancer patients were covered by Medicaid than non-cancer patients. Oppositely, more non-cancer patients were uninsured ($p < 0.0001$). Furthermore, cancer patients trended to report more chronic conditions than non-cancer patients (3.2 vs. 2.7; $p < 0.0001$). They also had a much higher incidence rate of chronic bronchitis, join pain and asthma. In addition, both groups had high percentage of self-report on HRQoL.

In the group of cancer patients with prescriptions, most of the individuals were older than 65 years (49.1%), female (60.3%), white (89%), non-Hispanic (94.4%), living in the South (38.4%) and city area (81.7%), and with high school diploma

(37.9%).

Table 6: Weighted Sample Characteristics of Cancer and Non-Cancer Populations: MEPS 2008

Characteristics	Cancer (N = 392)	Non-Cancer (N = 1,960)	P-Value	
Demographics				
Age (%)				
Mean (SE) Age, y	62.7 (0.76)	62.7 (0.51)	0.9997	
18-39 y	8.1	8.2	0.9187	
40-64 y	42.8	43.0	0.9678	
65+ y	49.1	48.8	0.9237	
Gender (%)				
Male	39.7	44.2	0.2098	
Female	60.3	55.8		
Race (%)				
White	89.0	83.9	0.0074	**
Black	8.3	10.3	0.1894	
Other [1]	2.7	5.8	0.0064	**
Ethnicity (%)				
Hispanic	5.6	9.5	0.0020	**
Non-Hispanic	94.4	90.5		
Marriage Status (%)				
Married	57.7	57.7	0.9940	
Unmarried [2]	42.3	42.3		
Region (%)				
Northeast	15.9	17.9	0.5375	
Midwest	24.8	22.2	0.3777	
South	38.4	39.4	0.7917	
West	20.9	20.5	0.8870	
Metropolitan Statistical Area (MSA) (%)				
MSA	81.7	81.9	0.9201	
Non-MSA	18.3	18.1		
Education (%)				
Mean (SE) Education, y	13.2 (0.14)	12.6 (0.10)	0.0005	**
Less 8 years	5.8	9.6	0.0292	*
High School	37.9	42.8	0.1471	
College	26.0	22.8	0.2728	
Above Bachelor	29.9	24.2	0.0781	

Notes:

[1] Other race included American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander.

[2] Not married included widowed, divorced, separated and never married.

P values are based on Chi-square test for categorical variables, T-test for continous variable.

SE: Standard Error.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Table 6 (continued):

Characteristics	Cancer (N = 392)	Non-Cancer (N = 19,067)	P-Value	
Income				
Personal Total Annual Income (%) [3]				
Low	31.0	32.0	0.6869	
Middle	7.0	9.6	0.1155	
High	62.0	58.4	0.2422	
Poverty Level (%)				
Poor	17.1	16.1	0.6533	
Low income	12.3	13.5	0.4925	
Middle income	25.3	30.7	0.0344	*
High income	45.4	39.6	0.0604	
Health Insurance Coverage (%) [4]				
Medicare	52.0	16.7	<.0001	**
Medicaid	11.1	9.7	0.3653	
Other Public Insurance [5]	6.6	3.4	0.0036	**
Private Insurance	64.9	66.6	0.5242	
Uninsured	2.3	16.3	<.0001	**
Prescription Insurance Status (%)				
Yes	54.5	57.2	0.3447	
No	45.5	42.8		
Currently Smoke (%)				
Yes	12.6	20.5	0.0025	**
No	86.8	77.9	0.0009	**
Chronic Conditions (%)				
Mean (SE) Chronic Conditions	3.2 (0.12)	1.6 (0.02)	<.0001	**
High Blood Pressure	54.0	30.6	<.0001	**
Coronary Heart Disease	15.9	5.5	<.0001	**
Angina	7.1	2.9	<.0001	**
Heart Attack	7.2	3.5	0.0018	**
Other Heart Disease	21.1	10.0	<.0001	**
Stroke	8.5	3.4	<.0001	**
Emphysema	6.0	2.3	<.0001	**
Chronic Bronchitis	8.8	2.2	<.0001	**
High Cholesterol	52.7	30.0	<.0001	**
Diabetes	19.7	9.3	<.0001	**
Joint Pain	54.3	31.5	<.0001	**
Arthritis	48.9	23.1	<.0001	**
Asthma	14.9	8.8	0.0008	**
Self Report (%)	91.2	90.0	0.4943	

Notes:

[3] Personal total income less than $15,000 was classifed as low income, between $15,000 and $20,000 was classified as middle income, above $20,000 was classified as high income.

[4] These categories are not mutually exclusive and a patient might be in multiple categories.

[5] Public insuracne included Tricare and Veterans.

P values are based on Chi-square test for categorical variables, T-test for continous variable.

SE: Standard Error.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Significant and consistent group differences by SES were also observed. Patients with higher personal annual income or lower poverty level were more likely to take medicines than patients with incomes below the poverty line. Half number of patients were Medicare beneficiaries (52%), and 64.9 percent had private insurance. Few of them were uninsured (2.3%), and less of them were non-prescription insurance beneficiaries (45.5%). As for chronic conditions, the most prevalent (almost above 50%) were high blood pressure, high cholesterol, joint pain and arthritis.

Table 7 compares lost productivity between cancer and non-cancer population. Cancer patients were less likely than non-cancer patients to have been employed in the past 12 months (employment status 43.3% vs. 47.3%; $p = 0.1731$), more likely to have work limit because of health problems (22.3% vs. 16.3%; $p = 0.0189$). The mean days lost from work in the past 12 months due to health problems were 3.1 days for cancer patients, 0.9 day for non-cancer patients ($p < 0.0001$). The days spent in bed in the past 12 months due to health problems for cancer patients were more than that for non-cancer patients (1.9 days vs. 0.9 day; $p < 0.0001$).

Table 7: Comparison of Lost Productivity Between Cancer and Non-Cancer Populations: MEPS 2008

Lost Productivity	Cancer (N = 392)	Non-Cancer (N = 1,960)	P-Value	
Employment Status				
Employed	43.3	47.3	0.1731	
Not Employed	56.7	52.7		
Work Limit due to Health Problem				
Yes	22.3	16.3	0.0189	*
No	4.1	3.7	0.7106	
Missing	73.6	80.0	0.0118	*
Days Lost from Work				
Mean (SE)	3.1 (0.65)	0.9 (0.19)	<.0001	**
Number of Bed Days				
Mean (SE)	1.9 (0.40)	0.9 (0.11)	<.0001	**

Notes:

P values are based on Chi-square test for categorical variables, T-test for continous variable.

SE: Standard Error.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

2.5.2 Health-related Quality of Life (HRQoL)

Pearson correlations among SF-12, K-6 and PHQ-2 are displayed in Table 8. There are a few evident trends from this data. Firstly, SF-12, K-6 and PHQ-2 were statistically significantly inter-correlated (all $p < 0.0001$). Secondly, with respect to the relationship between SF-12 and K-6, K-6 correlated the greatest with MCS-12 (coefficient $r = -0.67$). Role emotional (accomplished less emotional) and mental health (felt downhearted) correlated highly with K-6 ($r = -0.56$, $r = -0.60$, respectively). Thirdly, the correlation between MCS-12 and PHQ-2 was higher than moderate ($r = -0.50$). Finally, PHQ-2 and K-6 were highly correlated ($r = 0.66$).

Table 8: Pearson Correlations for the SF-12, K-6 and PHQ-2

	K-6		PHQ-2	
	Coefficient [1]	**P-Value [2]**	**Coefficient [1]**	**P-Value [2]**
SF-12				
PCS-12	-0.40	<.0001 **	-0.27	<.0001 **
MCS-12	-0.67	<.0001 **	-0.50	<.0001 **
General Health	0.40	<.0001 **	0.32	<.0001 **
Physical Functioning				
Activities	-0.31	<.0001 **	-0.18	<.0001 **
Limitations in Climbing Stairs	-0.29	<.0001 **	-0.15	<.0001 **
Role Physical				
Accomplished Less Physical	-0.44	<.0001 **	-0.26	<.0001 **
Limited in Work	-0.42	<.0001 **	-0.25	<.0001 **
Bodily Pain	0.41	<.0001 **	0.29	<.0001 **
Vitality Scale	0.44	<.0001 **	0.33	<.0001 **
Social Functioning	-0.48	<.0001 **	-0.31	<.0001 **
Role Emotional				
Accomplished Less Emotional	-0.56	<.0001 **	-0.35	<.0001 **
Work Less Carefully	-0.47	<.0001 **	-0.30	<.0001 **
Mental Health				
Felt Calm	0.43	<.0001 **	0.31	<.0001 **
Felt Downhearted	-0.60	<.0001 **	-0.40	<.0001 **
PHQ-2	0.66	<.0001 **	-	- -

Notes:

SF-12: Short Form-12; PCS: Physical Component Summary; MCS: Mental Component Summary; K-6: Kessler Index; PHQ-2: Patient Health Questionnaire.

[1] Coefficient larger than 0 indicates positive correlation; less than 0 indicates negative correlation; equal to 0 means no correlation.

[2] P-Values are determined using Pearson correlation.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Table 9 reports weighted mean SF-12, K-6 and PHQ-2 scores for demographic and socioeconomic characteristics.

Table 9: Weighted HRQoL Scores in Cancer and Non-Cancer Populations by Characteristics: MEPS 2008

Characteristics	PCS-12 [1]		MCS-12 [2]		K-6 [3]		PHQ-2 [4]	
	Cancer Mean (SE)	Non-Cancer Mean (SE)	Cancer Mean (SE)	Non-Cancer Mean (SE)	Cancer Mean (SE)	Non-Cancer Mean (SE)	Cancer Mean (SE)	Non-Cancer Mean (SE)
Overall	41.3 (0.77)	45.4 (0.39)	49.8 (0.62)	51.3 (0.33)	4.3 (0.29)	3.4 (0.11)	1.2 (0.12)	0.9 (0.05)
Age								
18-39 y	46.8 (1.49)	53.8 (0.62)	44.8 (1.36)	50.7 (0.62)	5.3 (0.91)	2.9 (0.26)	1.6 (0.28)	0.7 (0.07)
40-64 y	44.2 (1.07)	47.9 (0.51)	49.6 (0.80)	50.6 (0.44)	3.9 (0.33)	3.6 (0.15)	1.2 (0.18)	0.9 (0.06)
65+ y	37.9 (1.05)	41.8 (0.56)	50.9 (0.85)	51.9 (0.49)	4.5 (0.42)	3.4 (0.16)	1.2 (0.14)	0.9 (0.07)
Gender								
Female	42.2 (0.93)	44.3 (0.52)	49.7 (0.68)	50.5 (0.45)	4.2 (0.34)	3.7 (0.16)	1.2 (0.12)	0.9 (0.07)
Male	40.0 (1.22)	46.8 (0.47)	50.1 (1.11)	52.2 (0.41)	4.5 (0.44)	3.1 (0.15)	1.3 (0.22)	0.8 (0.06)
Race								
White	41.5 (0.84)	45.5 (0.43)	50.1 (0.68)	51.5 (0.37)	4.2 (0.31)	3.3 (0.12)	1.2 (0.13)	0.8 (0.05)
Black	39.6 (1.29)	44.2 (0.74)	47.4 (1.10)	50.0 (0.54)	5.2 (0.55)	4.3 (0.22)	1.8 (0.21)	1.5 (0.15)
Other [5]	40.4 (2.00)	46.1 (0.71)	48.6 (1.06)	50.5 (0.77)	5.0 (0.84)	3.5 (0.32)	1.2 (0.29)	0.9 (0.08)
Ethnicity								
Hispanic	41.0 (1.41)	46.5 (0.75)	47.0 (1.20)	50.0 (0.60)	6.1 (0.51)	3.9 (0.23)	2.1 (0.33)	0.9 (0.07)
Non-Hispanic	41.4 (0.79)	45.3 (0.41)	50.0 (0.63)	51.4 (0.34)	4.2 (0.30)	3.4 (0.11)	1.2 (0.12)	0.9 (0.06)
Marriage Status								
Married	42.8 (1.09)	46.6 (0.44)	50.8 (0.75)	52.6 (0.39)	3.7 (0.33)	3.0 (0.13)	1.0 (0.14)	0.6 (0.05)
Unmarried [6]	39.3 (1.01)	43.7 (0.60)	48.4 (0.99)	49.5 (0.51)	5.2 (0.48)	4.1 (0.18)	1.6 (0.20)	1.2 (0.09)
Region								
Northeast	40.4 (1.88)	47.4 (0.69)	50.7 (0.99)	51.3 (0.77)	4.7 (0.76)	3.3 (0.21)	1.3 (0.28)	0.9 (0.12)
Midwest	40.7 (1.07)	45.4 (0.91)	48.5 (1.33)	52.2 (0.50)	4.7 (0.50)	3.4 (0.23)	1.5 (0.22)	0.8 (0.10)
South	41.8 (1.37)	44.4 (0.64)	49.3 (0.88)	50.8 (0.49)	4.0 (0.49)	3.5 (0.16)	1.1 (0.21)	0.9 (0.09)
West	41.8 (1.60)	45.5 (0.55)	51.5 (1.22)	51.1 (0.67)	4.1 (0.54)	3.5 (0.22)	1.1 (0.16)	0.9 (0.08)
Metropolitan Statistical Area								
MSA	41.7 (0.87)	45.6 (0.40)	50.2 (0.72)	51.2 (0.34)	4.1 (0.31)	3.4 (0.11)	1.2 (0.15)	0.8 (0.06)
Non-MSA	39.6 (1.19)	44.3 (0.86)	48.2 (0.95)	51.6 (0.75)	5.6 (0.57)	3.6 (0.28)	1.4 (0.15)	1.0 (0.12)
Education								
Less 8 years	33.5 (1.37)	41.1 (0.64)	50.2 (1.47)	47.6 (0.69)	4.8 (0.56)	5.2 (0.32)	1.3 (0.25)	1.4 (0.11)
High School	40.2 (1.21)	43.6 (0.51)	49.7 (0.96)	50.8 (0.49)	4.6 (0.47)	3.8 (0.17)	1.4 (0.14)	1.0 (0.08)
College	39.4 (1.18)	46.3 (0.81)	47.7 (1.34)	51.9 (0.59)	5.2 (0.53)	3.0 (0.17)	1.2 (0.22)	0.7 (0.09)
Above Bachelor	45.7 (0.89)	49.3 (0.50)	51.7 (0.73)	52.7 (0.50)	3.2 (0.37)	2.5 (0.17)	1.0 (0.18)	0.6 (0.05)
Income								
Personal Total Annual Income [7]								
Low	37.5 (1.20)	41.3 (0.61)	47.5 (1.27)	49.7 (0.52)	5.5 (0.53)	4.5 (0.22)	1.7 (0.19)	1.2 (0.09)
Middle	41.0 (1.54)	44.1 (0.94)	47.7 (1.22)	50.7 (0.82)	5.1 (0.50)	3.7 (0.27)	1.2 (0.14)	1.0 (0.13)
High	43.3 (0.96)	47.8 (0.46)	51.2 (0.68)	52.2 (0.40)	3.7 (0.32)	2.8 (0.13)	1.0 (0.15)	0.7 (0.06)
Poverty Level								
Poor	35.1 (1.21)	40.5 (0.74)	47.0 (0.99)	49.6 (0.66)	6.4 (0.43)	4.6 (0.28)	1.9 (0.17)	1.4 (0.13)
Low income	40.0 (1.58)	42.2 (0.89)	49.7 (1.37)	49.6 (0.77)	4.3 (0.52)	4.2 (0.26)	1.1 (0.22)	1.2 (0.11)
Middle income	41.8 (1.34)	45.9 (0.56)	50.4 (1.09)	51.1 (0.51)	4.1 (0.45)	3.6 (0.19)	1.2 (0.16)	0.9 (0.09)
High income	43.8 (1.02)	48.0 (0.57)	50.6 (1.03)	52.7 (0.51)	3.7 (0.40)	2.5 (0.14)	1.0 (0.16)	0.5 (0.06)

Notes:

SF-12: Short Form-12; PCS: Physical Component Summary; MCS: Mental Component Summary; K-6: Kessler Index; PHQ-2: Patient Health Questionnaire; SE: Standard Error.

[1] Possible range for PCS-12 is from 0 to 100 with a higher score indicating a more impaired quality of life.

[2] Possible range for MCS-12 is from 0 to 100 with a higher score indicating a more impaired quality of life.

[3] Possible range for K-6 summary index is from 0 to 24 with a higher score indicating a more serious distress.

[4] Possible range for PHQ-2 summary score is from 0 to 6 with a higher score indicating a more serious depression.

[5] Other race included American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander.

[6] Not married included widowed, divorced, separated and never married.

[7] Personal total income less than $15,000 was classifed as low income, between $15,000 and $20,000 was classified as middle income, above $20,000 was classified as high income.

All were significant between cancer and non-cancer populations based on Z tests ($P < 0.05$).

Table 9 (continued):

Characteristics	PCS-12 [1]		MCS-12 [2]		K-6 [3]		PHQ-2 [4]	
	Cancer Mean (SE)	Non-Cancer Mean (SE)	Cancer Mean (SE)	Non-Cancer Mean (SE)	Cancer Mean (SE)	Non-Cancer Mean (SE)	Cancer Mean (SE)	Non-Cancer Mean (SE)
Health Insurance Coverage								
Medicare	37.6 (1.05)	41.4 (0.55)	50.5 (0.81)	51.5 (0.49)	4.7 (0.40)	3.6 (0.16)	1.3 (0.14)	1.0 (0.08)
Medicaid	37.0 (1.15)	37.9 (0.68)	43.8 (0.94)	45.0 (0.90)	6.9 (0.37)	6.3 (0.39)	2.1 (0.16)	1.9 (0.17)
Other Public Insurance [8]	42.0 (1.00)	39.5 (1.23)	51.7 (0.82)	49.7 (1.15)	3.9 (0.46)	4.4 (0.17)	1.3 (0.53)	1.3 (0.12)
Private Insurance	42.7 (0.94)	47.9 (0.45)	49.7 (0.83)	52.0 (0.40)	4.0 (0.37)	2.8 (0.13)	1.2 (0.16)	0.7 (0.05)
Uninsured	44.1 (1.62)	46.6 (0.76)	49.4 (1.85)	50.3 (0.45)	3.7 (0.64)	4.2 (0.24)	1.0 (0.29)	1.1 (0.12)
Prescription Insurance Status								
Yes	42.6 (1.01)	48.2 (0.49)	49.3 (0.87)	51.6 (0.44)	4.2 (0.38)	2.8 (0.12)	1.2 (0.17)	0.7 (0.05)
No	39.8 (1.10)	42.5 (0.55)	50.5 (0.84)	50.9 (0.44)	4.5 (0.41)	4.0 (0.17)	1.2 (0.16)	1.1 (0.08)
Currently Smoke								
Yes	40.6 (1.32)	45.3 (0.74)	47.7 (1.23)	49.3 (0.65)	6.0 (0.64)	4.4 (0.34)	1.4 (0.17)	1.1 (0.11)
No	41.4 (0.85)	45.5 (0.42)	50.1 (0.67)	51.7 (0.36)	4.1 (0.30)	3.2 (0.11)	1.2 (0.13)	0.8 (0.06)
Chronic Conditions								
High Blood Pressure	37.8 (0.97)	41.5 (0.54)	50.2 (0.78)	50.1 (0.51)	4.8 (0.41)	3.9 (0.17)	1.3 (0.15)	1.1 (0.08)
Coronary Heart Disease	33.0 (1.17)	37.5 (0.71)	48.0 (1.57)	47.7 (0.91)	6.4 (0.52)	5.2 (0.30)	2.0 (0.28)	1.5 (0.17)
Angina	31.4 (1.04)	36.7 (0.57)	47.5 (1.55)	48.0 (0.72)	5.9 (0.69)	5.8 (0.32)	1.6 (0.17)	1.6 (0.13)
Heart Attack	32.5 (1.46)	36.6 (0.69)	47.0 (2.22)	49.4 (0.75)	6.7 (0.58)	4.4 (0.23)	1.9 (0.33)	1.5 (0.08)
Other Heart Disease	38.0 (1.29)	40.4 (0.86)	51.0 (1.02)	49.4 (0.64)	4.8 (0.46)	4.6 (0.27)	1.5 (0.23)	1.2 (0.12)
Stroke	33.9 (1.21)	37.1 (0.90)	48.1 (1.43)	49.1 (0.51)	6.8 (0.55)	5.4 (0.28)	1.6 (0.18)	1.4 (0.13)
Emphysema	30.4 (1.04)	33.7 (0.82)	48.7 (0.86)	47.6 (0.79)	6.6 (0.67)	6.5 (0.49)	1.4 (0.23)	1.7 (0.20)
Chronic Bronchits	30.3 (1.66)	38.7 (1.23)	44.7 (1.12)	49.4 (0.93)	7.2 (0.54)	5.0 (0.29)	2.2 (0.18)	1.9 (0.26)
High Cholesterol	39.9 (1.08)	42.7 (0.50)	50.4 (0.91)	50.8 (0.48)	4.7 (0.46)	3.7 (0.15)	1.3 (0.17)	1.0 (0.07)
Diabetes	36.7 (1.48)	39.0 (0.82)	49.0 (1.33)	49.0 (0.75)	5.5 (0.58)	4.7 (0.31)	1.6 (0.20)	1.4 (0.13)
Joint Pain	37.9 (1.05)	40.8 (0.57)	49.3 (0.87)	49.8 (0.57)	4.8 (0.45)	4.3 (0.18)	1.3 (0.17)	1.1 (0.08)
Arthritis	36.7 (1.00)	39.2 (0.56)	49.7 (0.89)	50.0 (0.55)	5.1 (0.43)	4.3 (0.18)	1.4 (0.16)	1.1 (0.08)
Asthma	37.7 (1.18)	39.7 (0.87)	48.0 (0.59)	47.2 (1.00)	5.9 (0.38)	5.7 (0.30)	1.6 (0.13)	1.7 (0.21)
Self Report	42.3 (0.80)	45.9 (0.39)	50.4 (0.57)	51.5 (0.35)	4.0 (0.27)	3.3 (0.10)	1.1 (0.13)	0.8 (0.05)

Notes:

SF-12: Short Form-12; PCS: Physical Component Summary; MCS: Mental Component Summary; K-6: Kessler Index; PHQ-2: Patient Health Questionnaire; SE: Standard Error.

[1] Possible range for PCS-12 is from 0 to 100 with a higher score indicating a more impaired quality of life.

[2] Possible range for MCS-12 is from 0 to 100 with a higher score indicating a more impaired quality of life.

[3] Possible range for K-6 summary index is from 0 to 24 with a higher score indicating a more serious distress.

[4] Possible range for PHQ-2 summary score is from 0 to 6 with a higher score indicating a more serious depression.

[8] Other public insuracne were public insurance excluding Medicare and Medicaid.

All were significant between cancer and noncancer populations based on Z tests ($P < 0.05$).

As expected, individuals with cancer prescription medications had worse HRQoL than those without cancer. Specifically, cancer patients reported poorer physical or mental health, more serious physiologic distress or depression.

In this table, cancer patients with medications had significantly lower average overall component summary scores of SF-12 than patients without cancer (cancer 41.3 vs. non-cancer 45.4 for PCS-12; cancer 49.8 vs. non-cancer 51.3 for MCS-12, respectively), but the average K-6 and PHQ-2 scores were significantly higher (4.3 vs. 3.4 for K-6 scores; 1.2 vs. 0.9 for PHQ-2 scores, respectively). Similar results were found in most characteristics in each population subgroup, such as age, gender, race, ethnicity, marriage status, region, income, prescription insurance, currently smoking status and proxy report. In addition, cancer patients experiencing chronic conditions

reported worse physical health, more serious psychological distress or greater tendency towards physiologic depression.

For cancer patients with prescription medications, PCS-12, K-6 and PHQ-2 scores declined monotonically among older age groups, but MCS-12 scores did not. It was found that blacks, Hispanics, unmarried persons, persons not living in city area, persons with low income and persons currently smoking were more likely to report poor physical or mental health and had greater tendency towards physiologic distress and depression. For region, education or health insurance coverage, the pattern was less clear. Patients with prescription insurance had lower physical health scores and higher mental health and K-6 scores.

Table 10 shows significant differences between these two groups for SF-12, K-6, or PHQ-2 scores. All the mean scores were weighted. For the entire sample, cancer patients had lower mean scores on PCS-12 and MCS-12, higher mean scores on K-6 and PHQ-2 than the non-cancer subjects. All the differences were statistically significant ($p < 0.05$).

The weighted mean PCS-12 of cancer patients with medications was 41.3 (Standard Error (SE) = 0.77), which were significantly lower than those without cancer (45.4, SE = 0.39), that meant, medication use was associated with worse physical health. The same trend was noted for MSC-12, physical functioning, role physical, social functioning, role emotional scales and mental health (felt downhearted). But the different trend was noted for vitality scale and mental health (felt calm). The weighted mean general health and bodily pain scores of cancer patients with medications were higher than non-cancer patients (cancer 3.0 vs. non-cancer 2.7 for general health, 2.4 vs. 2.1 for bodily pain, $p < 0.0001$, respectively), which meant that cancer patients experienced worse general health and more pain. Among the eight domains, the differences observed in the role physical scales (limited in work) and bodily pain were particularly salient. Overall, these impairments were greater in physical than mental health.

It was also noted that cancer patients with medications experienced more serious psychological distress, and had greater tendency towards depression. The weighted

mean K-6 summary index score was 4.3 (SE = 0.29) for cancer patients, and 3.4 (SE = 0.11) for patients without cancer. The weighted mean summary score of PHQ-2 was 1.2 (SE = 0.12) for cancer patients, which was higher than that of non-cancer patients 0.9 (SE = 0.05). The same trend was noted for six subscales of K-6 and two subscales of PHQ-2.

Table 10: Differences in HRQoL Measures Between Cancer and Non-Cancer Populations: MEPS 2008

HRQoL Instruments	Cancer		Non-Cancer		Unadjusted Difference				Adjusted Difference [1]			
	Mean	SE	Mean	SE	Mean	SE	P-Value		Mean	SE	P-Value	
Short Form-12 (SF-12) [2]												
Physical Health Score (PCS-12)	41.3	0.77	45.4	0.39	-4.06	0.81	<.0001	**	-3.31	0.72	<.0001	**
Mental Health Score (MCS-12)	49.8	0.62	51.3	0.33	-1.44	0.68	0.0364	*	-1.34	0.67	0.0483	*
General Health	3.0	0.07	2.7	0.04	0.32	0.08	<.0001	**	0.32	0.07	<.0001	**
Physical Functioning												
Limitations in Moderate Activities	2.3	0.06	2.5	0.03	-0.24	0.07	0.0003	**	-0.20	0.07	0.0029	**
Limitations in Climbing Stairs	2.2	0.06	2.5	0.03	-0.23	0.08	0.0031	**	-0.18	0.08	0.0235	*
Role Physical												
Accomplished Less Physical	3.6	0.08	3.9	0.03	-0.32	0.09	0.0003	**	-0.23	0.09	0.0067	**
Limited in Work	3.6	0.08	4.0	0.04	-0.39	0.09	<.0001	**	-0.29	0.09	0.0012	**
Bodily Pain	2.4	0.07	2.1	0.05	0.35	0.09	<.0001	**	0.27	0.08	0.0016	**
Vitality Scale	3.0	0.08	2.7	0.04	0.32	0.08	0.0002	**	0.27	0.08	0.0008	**
Social Functioning	4.2	0.07	4.5	0.04	-0.28	0.08	0.0008	**	-0.24	0.08	0.0037	**
Role Emotional												
Accomplished Less Emotional	4.1	0.07	4.4	0.03	-0.27	0.08	0.0009	**	-0.26	0.08	0.0029	**
Work Less Carefully	4.2	0.07	4.4	0.04	-0.26	0.08	0.0011	**	-0.24	0.08	0.0040	**
Mental Health												
Felt Calm	2.5	0.07	2.4	0.04	0.09	0.08	0.2309		0.06	0.08	0.4286	
Felt Downhearted	4.1	0.07	4.2	0.03	-0.11	0.08	0.2054		-0.09	0.08	0.2865	
Kessler Index (K-6) [3]												
Summary Index	4.3	0.29	3.4	0.11	0.91	0.31	0.0034	**	0.86	0.28	0.0028	**
Felt Nervous	1.2	0.11	0.9	0.03	0.33	0.11	0.0028	**	0.29	0.11	0.0074	**
Felt Hopeless	0.8	0.10	0.5	0.03	0.28	0.11	0.0140	*	0.27	0.11	0.0149	*
Felt Restless or Fidgety	1.2	0.10	0.9	0.04	0.25	0.11	0.0244	*	0.22	0.11	0.0378	*
Felt Sad	0.7	0.11	0.4	0.03	0.25	0.11	0.0296	*	0.25	0.11	0.0236	*
Felt that Everything was an Effort	1.2	0.11	0.9	0.04	0.34	0.11	0.0023	**	0.31	0.11	0.0047	**
Felt Worthless	0.7	0.10	0.5	0.04	0.20	0.11	0.0770		0.19	0.11	0.0809	
Patient Health Questionnaire (PHQ-2) [4]												
Summary Score	1.2	0.12	0.9	0.05	0.37	0.13	0.0049	**	0.36	0.13	0.0048	**
Decreased Interest	0.8	0.10	0.5	0.04	0.29	0.11	0.0094	**	0.28	0.11	0.0108	*
Depressed Mood	0.8	0.11	0.5	0.03	0.29	0.11	0.0101	*	0.28	0.11	0.0110	*

Notes:

[1] Adjusted differences were estimated from multivariate regression models controlling for sociodemographic variables, current smoking status, prescription insurance status, chronic conditions, and proxy reporting.

[2] Possible range for PCS-12 is from 0 to 100 with a higher score indicating a more impaired quality of life. Possible range for MCS-12 is from 0 to 100 with a higher score indicating a more impaired quality of life. Possible range for physical functioning is from 1 to 3 with a higher score indicating less limitations. Possible range for the other subscales is from 1 to 5 with a higher score indicating better health. For general health perceptions and bodily pain, higher score indicates poor general health and aggravating pain.

[3] Possible range for K-6 summary index is from 0 to 24 with a higher score indicating a more serious distress.

[4] Possible range for PHQ-2 summary score is from 0 to 6 with a higher score indicating a more serious depression.

SE: Standard Error.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

The differences in the HRQoL scores became smaller after controlling for socio-demographic characteristics, prescription insurance status, current smoking status, chronic conditions, and proxy reporting. After adjustment, the marginal impact of patients with medications was highly statistically significant across all three HRQoL measures and all seemed to be clinically significant. Compared with mental function-related domains measured by the MCS-12, physical function-related domains measured by the PCS-12 showed a greater decrease in HRQoL (unadjusted difference: -4.06 for PCS-12 vs. -1.44 for MCS-12). The adjusted differences between cancer patients with prescription medications and non-cancer patients were -3.31 for PCS-12 (7.3% of the score in the non-cancer population), -1.34 for MCS-12 (2.6%), 0.86 for K-6 (25.3%), and 0.36 for PHQ-2 (40%).

Additionally, this study explored if differences arose in HRQoL scores of cancer patients with prescriptions across socio-demographic groups and categories dichotomized by health behaviors and chronic conditions. See Table 11.

It showed that younger age, more education, no prescription insurance coverage, no experience of chronic conditions, and self-reporting were significant predictors of a higher PCS-12 score. Younger age, Hispanic, less education, and lower income were significant risk factors, and self-reporting was a significantly mitigating factor for the MCS-12 score in the regression equation. Younger age, Hispanic, living in non-city area, less education, currently smoking, and experience of high cholesterol, and not self-reporting were significant predictors of higher K-6 scores, which indicated that these patients with greater tendency towards mental disability. White, Non-Hispanic and married, and self-reporting were significant predictors of lower PHQ-2 scores, which indicated that these patients had less serious depression. Overall, old age, less education attainment and chronic conditions were risk factors of HRQoL. Hispanics were more likely to report worse mental problems or more serious depression than non-Hispanics.

Table 11: Results of Multivariate Analysis of HRQoL on Cancer Patients with Prescription Medications [1]

Independent Variables	PCS-12				MCS-12				K-6				PHQ-2			
	Coefficient	SE	P-Value		Coefficient	SE	P-Value		Coefficient	SE	P-Value		Coefficient	SE	P-Value	
Age																
18-39 y	2.97	2.17	0.1763		-6.29	1.87	0.0013	**	1.58	0.72	0.0322	*	0.62	0.34	0.0733	
40-64 y	3.27	1.40	0.0222	*	-1.60	1.37	0.2455		-0.01	0.48	0.9887		0.31	0.16	0.0547	
65+ y reference	-	-	-		-	-	-		-	-	-		-	-	-	
Gender																
Female	1.03	1.19	0.3872		0.46	1.12	0.6819		-0.22	0.44	0.6274		-0.28	0.19	0.1427	
Male reference	-	-	-		-	-	-		-	-	-		-	-	-	
Race																
Black	0.16	1.64	0.9223		-2.60	1.41	0.0704		0.89	0.65	0.1785		0.56	0.27	0.0424	*
Other [2]	-0.12	1.56	0.9390		0.01	1.43	0.9935		0.67	0.92	0.4682		-0.41	0.53	0.4392	
White reference	-	-	-		-	-	-		-	-	-		-	-	-	
Ethnicity																
Hispanic	1.19	1.38	0.3926		-3.29	1.23	0.0093	**	2.41	0.81	0.0042	**	0.99	0.28	0.0007	**
Non-Hispanic reference	-	-	-		-	-	-		-	-	-		-	-	-	
Marriage Status																
Married	1.78	1.30	0.1736		1.94	0.99	0.0547		-0.84	0.48	0.0861		-0.64	0.19	0.0013	**
Unmarried [3] reference	-	-	-		-	-	-		-	-	-		-	-	-	
Region																
Northeast	0.42	1.93	0.8300		-1.34	1.62	0.4103		0.76	0.88	0.3914		0.06	0.24	0.8203	
Midwest	1.39	1.94	0.4744		-1.07	1.34	0.4263		-0.40	0.55	0.4691		0.10	0.27	0.7123	
South	0.59	1.66	0.7247		-1.55	1.41	0.2777		-0.36	0.48	0.4587		-0.07	0.20	0.7289	
West reference	-	-	-		-	-	-		-	-	-		-	-	-	
Metropolitan Statistical Area																
MSA	-1.57	1.25	0.2117		1.11	1.12	0.3248		-1.33	0.50	0.0095	**	-0.16	0.21	0.4530	
Non-MSA reference	-	-	-		-	-	-		-	-	-		-	-	-	
Education																
Less 8 years	-7.65	2.62	0.0048	**	1.44	1.91	0.4550		-0.84	0.94	0.3752		-0.30	0.25	0.2348	
High School	-3.37	1.16	0.0048	**	-1.29	1.10	0.2468		0.74	0.56	0.1894		0.22	0.22	0.3069	
College	-4.64	1.60	0.0050	**	-3.96	1.64	0.0187	*	1.75	0.49	0.0006	**	0.12	0.21	0.5759	
Above Bachelor reference	-	-	-		-	-	-		-	-	-		-	-	-	
Income																
Personal Total Annual Income [4]																
Low	-1.51	1.97	0.4464		-4.43	1.93	0.0251	*	0.75	0.66	0.2603		0.60	0.37	0.1045	
Middle	0.25	2.35	0.9170		-5.06	2.29	0.0307	*	1.45	0.83	0.0837		0.36	0.25	0.1506	
High reference	-	-	-		-	-	-		-	-	-		-	-	-	
Poverty Level																
Poor	-2.99	2.01	0.1428		1.87	2.31	0.4217		0.53	0.83	0.5222		-0.05	0.42	0.9059	
Low income	0.97	1.81	0.5918		2.66	1.99	0.1843		-1.09	0.75	0.1542		-0.55	0.36	0.1353	
Middle income	0.49	1.29	0.7049		1.36	1.17	0.2480		-0.69	0.47	0.1495		0.01	0.21	0.9647	
High income reference	-	-	-		-	-	-		-	-	-		-	-	-	

Notes:

SF-12: Short Form-12; PCS: Physical Component Summary; MCS: Mental Component Summary; K-6: Kessler Index; PHQ-2: Patient Health Questionnaire; SE: Standard Error.

[1] Adjusted for socio-demographic variables, prescription insurance status, current smoking status, chronic conditions and self-reporting.

[2] Other race included American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander.

[3] Not married included widowed, divorced, separated and never married.

[4] Personal total income less than $15,000 was classifed as low income, between $15,000 and $20,000 was classified as middle income, above $20,000 was classified as high income.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Table 11 (continued):

Independent Variables	PCS-12			MCS-12			K-6			PHQ-2		
	Coefficient	SE	P-Value	Coefficient	SE	P-Value	Coefficient	SE	P-Value	Coefficient	SE	P-Value
Prescription Insurance Status												
Yes	-2.81	1.21	0.0231 *	-1.18	1.08	0.2792	0.48	0.50	0.3404	0.23	0.15	0.1273
No reference	-	-	-	-	-	-	-	-	-	-	-	-
Currently Smoke												
Yes	-0.79	1.63	0.6321	-0.18	1.02	0.8628	2.10	0.51	0.0001 **	-0.05	0.24	0.8259
No reference	-	-	-	-	-	-	-	-	-	-	-	-
Chronic Conditions												
High Blood Pressure												
Yes	-4.36	1.21	0.0006 **	0.95	1.08	0.3840	0.05	0.47	0.9103	0.03	0.15	0.8199
No reference	-	-	-	-	-	-	-	-	-	-	-	-
High Cholesterol												
Yes	1.22	1.12	0.2781	0.08	1.20	0.9490	1.11	0.45	0.0162 *	0.05	0.17	0.7809
No reference	-	-	-	-	-	-	-	-	-	-	-	-
Joint Pain												
Yes	-3.98	1.35	0.0045 **	-2.31	1.17	0.0524	0.69	0.42	0.1001	0.27	0.17	0.1326
No reference	-	-	-	-	-	-	-	-	-	-	-	-
Arthritis												
Yes	-5.46	1.54	0.0007 **	0.43	1.08	0.6892	0.72	0.36	0.0508	0.19	0.15	0.2242
No reference	-	-	-	-	-	-	-	-	-	-	-	-
Self Report												
Yes	7.14	2.10	0.0011 **	6.40	1.86	0.0010 **	-3.17	0.88	0.0006 **	-0.75	0.29	0.0117 *
No reference	-	-	-	-	-	-	-	-	-	-	-	-

Notes:

SF-12: Short Form-12; PCS: Physical Component Summary; MCS: Mental Component Summary; K-6: Kessler Index; PHQ-2: Patient Health Questionnaire; SE: Standard Error.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

2.5.3 Total and Out-of-Pocket Prescription Medication Expenditures

This section includes the mean distributions of total and out-of-pocket prescription medication expenditures of cancer patients by characteristics. Then the results of multivariate analysis will be presented.

2.5.3.1 Mean Expenditures by Patient Characteristics

Table 12 presents weighted mean total and out-of-pocket expenditures by cancer patient characteristics. For cancer patients, the weighted mean total and out-of-pocket prescription medication expenditures were $3,169.1 (SD = 203.3) and $744.6 (SD = 59.8), respectively. Nonelderly patients had lower total and out-of-pocket spending than the elderly.

Table 12: Weighted Total and Out-of-Pocket Expenditure in Cancer Population with Prescription Medications by Characteristics: MEPS 2008

Characteristics	Total Expenditure		Out-of-Pocket Expenditure	
	Mean	SD	Mean	SD
Overall	3,169.1	203.3	744.6	59.8
Age				
18-39 y	1,797.8	466.5	428.0	121.3
40-64 y	2,418.5	324.1	579.0	79.9
65+ y	4,049.9	288.0	941.2	84.5
Gender				
Female	2,771.5	232.8	770.0	86.1
Male	3,772.3	361.9	706.0	62.1
Race				
White	3,265.0	223.4	766.1	65.4
Black	2,647.9	324.3	653.7	159.4
Other [1]	1,612.0	191.8	316.0	35.2
Ethnicity				
Hispanic	4,699.5	418.9	1,073.4	116.9
Non-Hispanic	3,078.0	213.0	725.0	63.3
Marriage Status				
Married	3,335.8	259.4	813.7	88.6
Unmarried [2]	2,941.5	313.1	650.3	63.0
Region				
Northeast	3,022.1	197.3	901.6	80.5
Midwest	3,304.5	346.6	656.2	77.8
South	3,616.6	446.1	728.6	102.5
West	2,298.8	263.0	759.4	193.2
Metropolitan Statistical Area				
MSA	3,203.5	219.8	680.7	51.5
Non-MSA	3,015.7	531.2	1,029.4	245.1
Education				
Less 8 years	4,545.7	619.2	866.5	231.5
High school	2,652.9	312.3	712.1	117.3
College	2,606.2	276.5	703.5	81.3
Above bachelor	4,015.7	388.2	794.6	75.9

Notes:

[1] Other race included American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander.

[2] Unmarried included widowed, divorced, separated and never married.

Table 12 (continued):

Characteristics	Total Expenditure		Out-of-Pocket Expenditure	
	Mean	SD	Mean	SD
Income				
Personal Total Annual Income [3]				
Low	3,509.9	376.7	841.9	130.7
Middle	2,977.0	542.9	729.1	199.5
High	3,020.4	225.0	697.7	50.9
Poverty Level				
Poor	2,619.2	278.7	541.6	41.3
Low income	3,476.2	488.1	1,022.9	291.2
Middle income	3,530.3	369.8	923.8	93.7
High income	3,091.2	296.3	645.6	61.3
Health Insurance Coverage				
Medicare				
Yes	4,189.4	305.4	961.6	88.4
No	2,061.9	200.0	509.1	53.0
Medicaid				
Yes	3,044.0	347.8	356.5	127.8
No	3,184.8	219.2	793.2	64.8
Other Public Insurance [4]				
Yes	3,502.2	1,252.9	652.2	132.0
No	3,145.6	198.6	751.1	63.3
Private Insurance				
Yes	3,389.8	297.5	736.5	86.2
No	2,760.7	205.2	759.6	68.0
Uninsured				
Yes	2,083.6	1,103.0	487.9	190.4
No	3,195.0	208.4	750.7	61.2
Prescription Insurance Status				
Yes	3,623.4	311.4	678.4	65.7
No	2,625.7	186.6	823.7	91.4
Currently Smoke				
Yes	2,550.7	535.3	515.4	112.0
No	3,258.3	209.4	777.7	64.4
Chronic Conditions				
High Blood Pressure				
Yes	4,204.4	329.4	1,007.7	93.5
No	1,952.9	189.3	435.5	50.6
High Cholesterol				
Yes	3,697.7	285.7	896.3	66.1
No	2,580.5	206.5	575.7	92.0
Joint Pain				
Yes	3,356.3	301.2	798.5	64.1
No	2,946.8	204.1	680.6	95.2
Arthritis				
Yes	3,630.8	347.8	849.8	73.4
No	2,727.5	184.7	644.0	87.6

Notes:

[3] Personal total income less than $15,000 was classifed as low income, between $15,000 and $20,000 was classified as middle income, above $20,000 was classified as high income.

[4] Other public insuracne were public insurance excluding Medicare and Medicaid.

As shown in Table 12, of the total expenditures, elderly, male, white, Hispanic, married, and living in city area persons had higher expenditures than young, female, black or other races, non-Hispanic, unmarried, and living in non-city area persons did. For region, education or income, the pattern of mean total spending was less clear.

Mean total expenditures paid by different source of payments were quite different. Patients covered by Medicare, private, other public or prescription insurance paid higher than those without Medicare, private, other public or prescription insurance coverage. Medicare patients paid higher total money for prescription medications in comparing with other insurance groups. Non-Medicaid beneficiaries spent more money for their medicine treatments in comparison to those of Medicaid covered. Uninsured individuals had much higher payment than those having insurance did.

Currently smokers had lower mean total prescription expenditure than former smokers. But patients reported chronic conditions had higher mean total prescription expenditure than their counterparts.

The same situations were also found in out-of-pocket spending, except that female or persons living in non-city area, patients covered with private, other public or prescription insurance had higher payment than their corresponding counterparts did.

2.5.3.2 Multivariate Analysis

As a result of the non-normal distribution of expenses, a logarithmic transformation was applied for correction to determine total and out-of-pocket prescription expenditures. Table 13 and Table 14 present the results of the multivariate regression of logarithmic transformation of expenditures.

Table 13: Factors Affecting Total Prescription Medication Expenditures by Cancer Patients: MEPS 2008 [1]

Parameter	Log (Total Expenditures +1)					
	Regression Coefficient	SE	Exponent Regression Coefficient $(e^{\beta}-1)*100$	95% CI	P-Value T-Test	P-Value Wald F
Intercept	5.67	0.98		(3.71 - 7.62)	<.0001 **	
Age						0.0553
18-39 y	-0.37	0.33	-30.93	(-1.03 - 0.28)	0.2578	
40-64 y	-0.54	0.22	-41.73	(-0.98 - -0.10)	0.0167 *	
65+ y [reference]	-	-	-	-	-	
Gender						0.1295
Female	0.20	0.13	22.14	(-0.06 - 0.47)	0.1295	
Male [reference]	-	-	-	-	-	
Race						0.5172
Black	-0.03	0.16	-2.96	(-0.35 - 0.29)	0.8476	
Other [2]	-0.24	0.21	-21.34	(-0.67 - 0.19)	0.2662	
White [reference]	-	-	-	-	-	
Ethnicity						0.3624
Hispanic	0.19	0.21	20.92	(-0.23 - 0.61)	0.3624	
Non-Hispanic [reference]	-	-	-	-	-	
Marriage Status						0.8516
Married	-0.02	0.12	-1.98	(-0.26 - 0.21)	0.8516	
Unmarried [3] [reference]	-	-	-	-	-	
Region						0.0302 *
Northeast	0.62	0.23	85.89	(0.17 - 1.08)	0.0077 **	
Midwest	0.60	0.21	82.21	(0.19 - 1.02)	0.0054 **	
South	0.52	0.22	68.20	(0.09 - 0.96)	0.0183 *	
West [reference]	-	-	-	-	-	
Metropolitan Statistical Area						0.5366
MSA	0.12	0.19	12.75	(-0.26 - 0.49)	0.5366	
Non-MSA [reference]	-	-	-	-	-	
Education						0.0704
Less 8 years	0.11	0.23	11.63	(-0.36 - 0.57)	0.6526	
High School	-0.31	0.16	-26.66	(-0.63 - 0.02)	0.0630	
College	-0.40	0.20	-32.97	(-0.80 - -0.00)	0.0492 *	
Above Bachelor [reference]	-	-	-	-	-	
Income						
Personal Total Annual Income [4]						0.0264 *
Low	0.50	0.18	64.87	(0.14 - 0.85)	0.0074 **	
Middle	0.05	0.18	5.13	(-0.31 - 0.42)	0.7719	
High [reference]	-	-	-	-	-	

Notes:

SF-12: Short Form-12; PCS: Physical Component Summary; MCS: Mental Component Summary; K-6: Kessler Index; PHQ-2: Patient Health Questionnaire; SE: Standard Error; CI: Confidence Intervals.

[1] Adjusted for socio-demographic variables, insurance coverage, prescription insurance status, current smoking status, chronic conditions and HRQoL scores.

[2] Other race included American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander.

[3] Not married included widowed, divorced, separated and never married.

[4] Personal total income less than $15,000 was classifed as low income, between $15,000 and $20,000 was classified as middle income, above $20,000 was classified as high income.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Table 13 (continued):

Parameter	Log (Total Expenditures +1)					
	Regression Coefficient	SE	Exponent Regression Coefficient $(e^{\beta}-1)*100$	95% CI	P-Value T-Test	P-Value Wald F
Poverty Level						0.0002 **
Poor	-0.65	0.22	-47.80	(-1.10 - -0.21)	0.0044 **	
Low income	-0.35	0.21	-29.53	(-0.77 - 0.07)	0.1015	
Middle income	0.16	0.15	17.35	(-0.14 - 0.46)	0.2986	
High income [reference]	-	-	-	-	-	
Health Insurance Coverage						0.0563
Medicare	0.31	0.22	36.34	(-0.13 - 0.76)	0.1619	
Medicaid	-0.15	0.30	-13.93	(-0.74 - 0.44)	0.6136	
Other Public Insurance [5]	-0.37	0.29	-30.93	(-0.96 - 0.21)	0.2074	
Uninsured	-0.42	0.59	-34.30	(-1.60 - 0.76)	0.4768	
Private Insurance [reference]	-	-	-	-	-	
Prescription Insurance Status						0.0029 **
Yes	0.45	0.14	56.83	(0.16 - 0.74)	0.0029 **	
No [reference]	-	-	-	-	-	
Currently Smoke						0.4640
Yes	-0.27	0.31	-23.66	(-0.89 - 0.34)	0.3802	
No [reference]	-	-	-	-	-	
Chronic Conditions						
High Blood Pressure						<.0001 **
Yes	0.75	0.18	111.70	(0.39 - 1.10)	<.0001 **	
No [reference]	-	-	-	-	-	
High Cholesterol						0.0093 **
Yes	0.41	0.15	50.68	(0.10 - 0.71)	0.0093 **	
No [reference]	-	-	-	-	-	
Joint Pain						0.0136 *
Yes	0.39	0.15	47.70	(0.08 - 0.69)	0.0136 *	
No [reference]	-	-	-	-	-	
Arthritis						0.1254
Yes	-0.22	0.14	-19.75	(-0.50 - 0.06)	0.1254	
No [reference]	-	-	-	-	-	
HRQoL						
PCS-12	-0.03	0.01	-2.96	(-0.04 - -0.02)	<.0001 **	
MCS-12	0.02	0.01	2.02	(-0.00 - 0.05)	0.0689	
K-6	0.04	0.02	4.08	(-0.00 - 0.09)	0.0692	
PHQ-2	0.08	0.04	8.33	(-0.01 - 0.17)	0.0843	

Notes:

[5] Other public insuracne were public insurance excluding Medicare and Medicaid.

SE: Standard Error; CI: Confidence Intervals.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Factors Affecting Total Prescription Medication Expenditures by Cancer Patients

After adjusting for differences in patients' age, gender, race, ethnicity, marital status, education, income, insurance coverage status, currently smoking status, chronic conditions and HRQoL scores in regression model, age was significantly associated with total prescription medication expenditures. Patients above 65 years old were the reference group. The total expenditures paid in patients between 40-64 years old were 41.73% ($p = 0.0167$) lower than that in elderly group (age > 65). It meant that total expenditures increased with age groups after controlling all the other variables. Total expenditures for patients living in the Northeast, Midwest, or South were higher than patients living in the West ($p < 0.05$). Total expenditures spent on patients with college-level education were 32.97% ($p = 0.0492$) lower than patients with the highest education level (above bachelor). Patients with poor family poverty level paid 47.8% ($p = 0.0044$) lower total expenditures than those with high income family poverty level, while patients with low personal total annual income paid 64.87% ($p = 0.0074$) higher total expenditures than those with high personal total annual income.

As shown in Table 13, patients covered with prescription insurance, their expenditures paid for prescription medicines were 56.83% higher than those for patients without prescription insurance ($p = 0.0029$). With regard to HRQoL, only PCS-12 was significantly associated with total medication expenditures (coefficient -0.03; $p < 0.0001$). It meant that patients who reported lower physical SF-12 scores paid higher medicine spending.

Seven variables presented significant association with total prescription medicine expenditures by Wald F statistic method, which tested the main effect of each predictor in regression mode. They were region ($p = 0.0302$), personal total annual income ($p = 0.0264$), poverty level ($p = 0.0002$), prescription insurance status ($p = 0.0029$), high blood pressure ($p < 0.0001$), high cholesterol ($p = 0.0093$) and joint pain ($p = 0.0136$). After controlling for contributing factors in regression model, region was significantly associated with total expenditures. Cancer patients who lived in the West had significantly lower prescription medicine total spending than those who did

not live there. Income was also significantly associated with expenditures in the predictive model. For patients whose total personal income was low, they paid much more total prescription medicine expenditures than that of higher personal income patients. Patients experienced high cholesterol, joint pain and arthritis had higher prescription medicine total spending that those without these chronic conditions.

Factors Affecting Out-of-Pocket Prescription Medication Expenditures by Cancer Patients

Table 14 shows that region, education, health insurance coverage, chronic conditions and HRQoL scores were significantly associated with out-of-pocket prescription medication expenditures, after adjusting for confounding factors in regression model. Patients living in the West had significantly lower medication out-of-pocket spending than those in other regions. The difference was greatest in patients living in the Northeast, who paid 105.44 percent higher out-of-pocket prescription medicine expenditures than patients living in the West ($p = 0.0018$). Patients with college education level paid 30.93 percent lower out-of-pocket expenditures than those with above bachelor level degrees ($p = 0.0408$). Patients covered with Medicaid, their expenditure paid for prescription medicines via out-of-pocket was 79.4% lower than that of the patients who purchased private insurance ($p < 0.0001$). The difference was even greater in other public insurance groups; it was 83.96 percent less ($p = 0.0058$). Patients experienced high blood pressure, high cholesterol and joint pain paid more out-of-pocket prescription medicines than those without these conditions ($p < 0.005$). Oppositely, patients reported arthritis had 27.39% lower out-of-pocket spending than those without arthritis ($p = 0.0484$).

The coefficients for the PCS-12 and the MCS -12 for this model were -0.03 ($p < 0.0001$) and 0.03 ($p = 0.0073$), respectively. The coefficient for the PHQ-2 for this model was 0.12 ($p = 0.005$).

By Wald F statistic method, region, poverty level, health insurance coverage, currently smoking status and chronic conditions presented significant association with out-of-pocket prescription medication expenditures. Patients with poor/low family

income paid lower out-of-pocket expense than those with the high family income. Former smokers paid much more than current smokers.

Table 14: Factors Affecting Out-of-Pocket Prescription Medication Expenditures by Cancer Patients: MEPS 2008[1]

Parameter	Log (Out-of-Pocket Expenditures +1)						
	Regression Coefficient	SE	Exponent Regression Coefficient $(e^{\beta}-1)*100$	95% CI	P-Value T-Test		P-Value Wald F
Intercept	5.32	0.82		(3.69 - 6.95)	<.0001	**	
Age							0.2401
18-39 y	0.05	0.26	5.13	(-0.47 - 0.58)	0.8354		
40-64 y	-0.25	0.19	-22.12	(-0.63 - 0.14)	0.2109		
65+ y reference	-	-	-	-	-		
Gender							0.2439
Female	0.16	0.13	17.35	(-0.11 - 0.42)	0.2439		
Male reference	-	-	-	-	-		
Race							0.9393
Black	0.01	0.20	1.01	(-0.40 - 0.41)	0.9705		
Other [2]	-0.07	0.21	-6.76	(-0.49 - 0.35)	0.7413		
White reference	-	-	-	-	-		
Ethnicity							0.6404
Hispanic	0.09	0.20	9.42	(-0.30 - 0.49)	0.6404		
Non-Hispanic reference	-	-	-	-	-		
Marriage Status							0.4809
Married	0.07	0.11	7.25	(-0.14 - 0.29)	0.4809		
Unmarried [3] reference	-	-	-	-	-		
Region							0.0183 *
Northeast	0.72	0.22	105.44	(0.28 - 1.17)	0.0018	**	
Midwest	0.45	0.22	56.83	(0.02 - 0.88)	0.0418	*	
South	0.53	0.22	69.89	(0.09 - 0.96)	0.0176	*	
West reference	-	-	-	-	-		
Metropolitan Statistical Area							0.2729
MSA	-0.19	0.17	-17.30	(-0.53 - 0.15)	0.2729		
Non-MSA reference	-	-	-	-	-		
Education							0.1665
Less 8 years	-0.28	0.30	-24.42	(-0.87 - 0.31)	0.3419		
High School	-0.26	0.15	-22.89	(-0.57 - 0.05)	0.0948		
College	-0.37	0.18	-30.93	(-0.72 - -0.02)	0.0408	*	
Above Bachelor reference	-	-	-	-	-		

Notes:

[1] Adjusted for socio-demographic variables, insurance coverage, prescription insurance status, current smoking status, chronic conditions and HRQoL scores.

[2] Other race included American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander.

[3] Not married included widowed, divorced, separated and never married.

[4] Personal total income less than $15,000 was classifed as low income, between $15,000 and $20,000 was classified as middle income, above $20,000 was classified as high income.

SE: Standard Error; CI: Confidence Intervals.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Table 14 (continued):

Parameter	Log (Out-of-Pocket Expenditures +1)							
	Regression Coefficient	SE	Exponent Regression Coefficient $(e^{\beta}$ -1) *100	95% CI	P-Value T-Test		P-Value Wald F	
Income								
Personal Total Annual Income [4]							0.8827	
Low	0.11	0.23	11.63	(-0.35 - 0.58)	0.6301			
Middle	0.05	0.21	5.13	(-0.37 - 0.48)	0.7977			
High [reference]	-	-	-	-	-			
Poverty Level							0.0307	*
Poor	-0.28	0.24	-24.42	(-0.77 - 0.20)	0.2429			
Low income	-0.39	0.26	-32.29	(-0.90 - 0.12)	0.1312			
Middle income	0.28	0.14	32.31	(-0.01 - 0.56)	0.0585			
High income [reference]	-	-	-	-	-			
Health Insurance Coverage							<.0001	**
Medicare	-0.25	0.25	-22.12	(-0.75 - 0.25)	0.3178			
Medicaid	-1.58	0.29	-79.40	(-2.16 - -1.00)	<.0001	**		
Other Public Insurance [5]	-1.83	0.64	-83.96	(-3.11 - -0.55)	0.0058	**		
Uninsured	-0.17	0.50	-15.63	(-1.17 - 0.84)	0.7402			
Private Insurance [reference]	-	-	-	-	-			
Prescription Insurance Status							0.0687	
Yes	-0.23	0.12	-20.55	(-0.47 - 0.02)	0.0687			
No [reference]	-	-	-	-	-			
Currently Smoke							0.0490	*
Yes	-0.35	0.25	-29.53	(-0.84 - 0.14)	0.1609			
No [reference]	-	-	-	-	-			
Chronic Conditions								
High Blood Pressure							0.0020	**
Yes	0.49	0.15	63.23	(0.19 - 0.80)	0.0020	**		
No [reference]	-	-	-	-	-			
High Cholesterol							0.0024	**
Yes	0.41	0.13	50.68	(0.15 - 0.68)	0.0024	**		
No [reference]	-	-	-	-	-			
Joint Pain							0.0117	*
Yes	0.35	0.14	41.91	(0.08 - 0.62)	0.0117	*		
No [reference]	-	-	-	-	-			
Arthritis							0.0484	*
Yes	-0.32	0.16	-27.39	(-0.63 - -0.00)	0.0484	*		
No [reference]	-	-	-	-	-			
HRQoL								
PCS-12	-0.03	0.00	-2.96	(-0.04 - -0.03)	<.0001	**		
MCS-12	0.03	0.01	3.05	(0.01 - 0.04)	0.0073	**		
K-6	0.01	0.02	1.01	(-0.03 - 0.05)	0.6635			
PHQ-2	0.12	0.04	12.75	(0.04 - 0.21)	0.0050	**		

Notes:

SF-12: Short Form-12; PCS: Physical Component Summary; MCS: Mental Component Summary; K-6: Kessler Index; PHQ-2: Patient Health Questionnaire; SE: Standard Error; CI: Confidence Intervals.

[5] Other public insuracne were public insurance excluding Medicare and Medicaid.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

2.5.3.3 Mean Predicted Total and Out-of-Pocket Prescription Medication Expenditures

Table 15 describes the results from multivariate regression models of predicted prescription medication expenditures associated with cancer patients. There was a strong relationship among predicted direct expenditure and demographic characteristics, insurance coverage, currently smoking status and chronic conditions.

After adjustment, the predicted annual mean total and out-of-pocket prescription medication expenditures associated with cancer were $2,572.1 and $597.1 respectively. Total and out-of-pocket expenditures significantly increased with age ($p < 0.0001$). Elderly patients (age $\geq$ 65) spent an average of $4,480.8 total expenditure ($873.5 for out-of-pocket prescription expenditure) compared with $1,205.5 for patients between 18-39 years old ($322.2 for out-of-pocket prescription expenditure) and $1,684.8 for patients between 40-64 years old ($456.1 for out-of-pocket prescription expenditure). With regard to race, whites had higher out-of-pocket spending than blacks and other races. More specifically, it was found that whites had a decrease in out-of-pocket spending by $102.5 in comparison to blacks, and $176.9 in comparison to other races. Compared with patients living in the Midwest, South or West, patients living in the Northeast paid almost twice as much as the total and out-of-pocket prescription expense. Among the four regions, patients living in the West incurred least prescription expense. Patients living in the Northeast paid an average of $4,374.1 ($p < 0.0001$) total expenditures, compared with $1,588.7 for the patients living in the West, In addition, patients living in MSA paid less total expenditures than those living non-MSA ($2,495.7 vs. $2,495.7; $p = 0.0415$). The same trend was found in out-of-pocket expenditures.

Table 15: Results of Regression Analysis to Estimate Predicted Total and Out-of-Pocket Prescription Medication Expenditures: MEPS 2008

Parameter	Total Expenditures			Out-of-Pocket Expenditures		
	Estimate	P-Value		Estimate	P-Value	
Overall	2,572.1			597.1		
Age						
18-39 y	1,205.5	<.0001	**	322.2	<.0001	**
40-64 y	1,684.8	<.0001	**	456.1	<.0001	**
65+ y	4,480.8	<.0001	**	873.5	<.0001	**
Gender						
Female	2,469.4	0.1404		572.0	0.0778	
Male	2,751.2			641.1		
Race						
White	2,630.2	0.2845		625.1	0.0347	*
Black	2,510.3	0.4588		522.6	0.0969	
Other [1]	1,898.2	0.1690		448.2	0.1037	
Ethnicity						
Hispanic	2,651.1	0.4345		494.0	0.1917	
Non-Hispanic	2,561.7			612.5		
Marriage Status						
Married	2,449.0	0.1398		613.3	0.3321	
Unmarried [2]	2,738.8			577.1		
Region						
Northeast	4,374.1	<.0001	**	1,025.2	<.0001	**
Midwest	2,770.7	0.1709		588.0	0.4794	
South	2,665.3	0.3245		652.0	0.0708	
West	1,588.7	<.0001	**	370.6	<.0001	**
Metropolitan Statistical Area						
MSA	2,495.7	0.0415	*	561.6	0.0005	**
Non-MSA	2,925.5			776.3		
Education						
Less 8 years	4,705.7	<.0001	**	694.2	0.0506	
High school	2,532.4	0.4577		589.3	0.4085	
College	2,217.7	0.0474	*	528.9	0.0824	
Above bachelor	2,419.5	0.1627		644.4	0.3054	

Notes:

[1] Other race included American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander.

[2] Unmarried included widowed, divorced, separated and never married.

[3] Personal total income less than $15,000 was classifed as low income, between $15,000 and $20,000 was classified as middle income, above $20,000 was classified as high income.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Table 15 (continued):

Parameter	Total Expenditures			Out-of-Pocket Expenditures		
	Estimate	P-Value		Estimate	P-Value	
Income						
Personal Total Annual Income [3]						
Low	3,043.0	0.0046	**	557.0	0.2899	
Middle	2,087.3	0.1276		447.7	0.0299	*
High	2,379.7	0.0310	*	655.9	0.0531	
Poverty Level						
Poor	2,421.9	0.3689		517.4	0.1551	
Low income	2,715.0	0.3134		492.8	0.0399	*
Middle income	3,229.1	0.0023	**	812.2	<.0001	**
High income	2,180.1	0.0031	**	554.5	0.0420	*
Health Insurance Coverage						
Medicare						
Yes	4,365.0	<.0001	**	870.2	<.0001	**
No	1,499.1			406.6		
Medicaid						
Yes	2,721.0	0.2914		399.0	0.0019	**
No	2,541.1			651.2		
Other Public Insurance [4]						
Yes	2,557.9	0.4985		412.7	0.0400	*
No	2,573.1			612.5		
Private Insurance						
Yes	2,348.9	0.0046	**	653.4	0.0876	
No	2,947.2			521.7		
Uninsured						
Yes	660.6	<.0001	**	370.4	0.0106	*
No	2,715.8			608.7		
Prescription Insurance Status						
Yes	2,423.3	0.0624		605.9	0.3284	
No	2,730.0			588.5		
Currently Smoke						
Yes	1,707.7	0.0003	**	386.5	<.0001	**
No	2,789.0			653.0		
Chronic Conditions						
High Blood Pressure						
Yes	4,443.1	<.0001	**	899.8	<.0001	**
No	1,314.1			360.9		
High Cholesterol						
Yes	3,914.2	<.0001	**	842.1	<.0001	**
No	1,660.7			417.4		
Joint Pain						
Yes	3,477.9	<.0001	**	729.6	<.0001	**
No	1,866.1			482.6		
Arthritis						
Yes	3,407.0	<.0001	**	682.3	0.0028	**
No	1,947.3			523.3		

Notes:

[4] Other public insuracne were public insurance excluding Medicare and Medicaid.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Low education level (less than 8 years) and low personal-income patients spent an average of $4,705.7 ($p < 0.0001$) and $3,043 ($p = 0.0046$) total expenditures, respectively, compared with $2,217.7 ($p = 0.0474$) for the patients with college education level, and $2,379.7 ($p = 0.0310$) for high personal-income patients. Patients with middle income poverty level paid much higher than those with other poverty levels. For total expenditures, patients with high income poverty level spent less than those with poor/low poverty level. But for out-of-pocket expenditures, the trend was opposite.

With regard to health insurance, persons covered by Medicare insurance paid higher total and out-of-pocket money for prescription medicine in comparing with other insurance groups. Medicare beneficiaries spent much higher average expense than those in the non-Medicare population (Medicare $4,365 vs. non-Medicare $1499.1 for total spending, $870.2 vs. $406.4 for out-of-pocket; $p < 0.0001$). Patients covered with private insurance paid less total prescription spending than their counterparts ($2348.9 vs. $2947.2; $p = 0.0046$). Other public insurance beneficiaries had a lower average out-of-pocket prescription spending than those with other public insurance ($412.7 vs. $612.5; $p = 0.04$). In addition, patients enrolled under Medicaid had a lower average out-of-pocket prescription spending than those without Medicaid ($399 vs. $651.2; $p = 0.0019$). Uninsured patients had a predicted average total expenditure of $660.6 ($370.4 for out-of-pocket) compared with $2,715.8 ($608.7 for out-of-pocket) for insured patients. Although the total prescription expenditures in prescription insurance beneficiaries ($2,423.3) was lower than that in non-prescription insurance population ($2,730), it was not significant ($p = 0.0624$).

Patients who were current smokers spent less than those who were former smokers ($1,707.7 vs. $2,789 for total expenditure, $p = 0.0003$; $386.5 vs. $653 for out-of-pocket expenditure, $p < 0.0001$). Patients experienced high blood pressure, high cholesterol, joint pain or arthritis had higher mean predicted total and out-of-pocket expenditures than patients without these chronic conditions ($p < 0.005$).

2.6 Discussion

This cross-sectional study examined the association of factors related to cancer prescription medication use, health-related quality of life (HRQoL), and prescription medication expenditures in the United States. Due to the differences in statistical analyses, HRQoL measures, socio-demographic characteristics of the sample and medical conditions selected, the findings of this study are not directly comparable to prior literature review. Nevertheless, a few differences and common findings are noteworthy. This section begins by presenting the major findings based on the outcomes obtained from the current study. Then the limitations and health policy implications will be discussed.

2.6.1 Major Findings

Firstly, this study examined the difference of HRQoL measures between cancer patients with prescription medications and age-matched non-cancer patients. The dependent variable - HRQoL, was measured by using self-reported scores on the measures of the 12-item Short Form Health Survey (SF-12), the Kessler Index (K-6) for general psychological distress, and the Patient Health Questionnaire (PHQ-2) for depression. It was found that compared with age-matched non-cancer patients, cancer patients with medications had impaired HRQoL. It was also found that cancer patients with medications had considerably lower subscale scores for the SF-12 and higher subscale scores in the K-6 and the PHQ-2, compared with the age-matched non-cancer patients. Specifically, cancer patients reported worse physical or mental health, more serious psychological distress and depression. These impairments were greater in physical than mental health.

It is generally believed that the small differences in HRQoL may be statistically significant but unimportant.[123] The clinically important difference (CID) reflects the amount of change in HRQoL that is meaningful to patients and their health care providers, this change could be either improvement or decline.[124] Minimal clinically important difference (MCID) is generally linked to the smallest difference in a HRQoL score that is considered to be clinically important.[123] The estimate of CID depends on

the assessment method and may possibly change for different questionnaires, population and context.[124] The 3 to 5 point difference in SF-36 scale scores is noted as the MCID translates into a 0.09 - 0.28 effect size range,[123] and it is considered large enough to be important. The current study revealed that of the summary measures of SF-12, only the PCS-12 showed a small effect. The effect size for MCS-12 did not indicate any practical significance. It was also noted that for cancer patients with prescriptions, the mean K-6 summary index score was 4.3, which was well below the optimal cut point (13) for the prevalence of serious mental illness in the national population.[117] It was the same with PHQ-2 score when the mean score 1.2 was well below the optimal cut point (3) for screening purposes.[118] Nevertheless, these data support the view that cancer is a traumatic event producing negative impact on various dimensions of a patient's HRQoL.[44]

In this study, the HRQoL was measured by three generic HRQoL measurements, the SF-12, the K-6 and the PHQ-2. All of them are suitable to a wide range of diseases and health conditions. The SF-12, the K-6 and the PHQ-2 measure a person's health status over the past four weeks, 30 days and two weeks, respectively. The advantage of the SF-12 includes its broad coverage of HRQoL dimensions; the advantages of the K-6 and the PHQ-2 are that they are simple, easy to complete, and could be used to compare different populations. In addition, the K-6 could sensitively measure the general distress severity in the range that are commonly found in clinical data.[112] Correlations among the SF-12 , the K-6 and the PHQ-2 were reported to be less than 0.50 (a high correlation[125]), except for the correlations between K-6 summary index and MCS-12 (0.67) / accomplished less emotional (0.56) / felt downhearted (0.60), PHQ-2 summary index and K-6 summary index (0.66) / MCS-12 (0.50). Due to the different attributes of these instruments, it was evident that the measurement of HRQoL using the SF-12, the K-6 and the PHQ-2 presented more meaningful information than only using one of the instruments. This study showed that compared with age-matched non-cancer population, all instruments reported impairments in comparable dimensions for cancer patients with prescription medications. Specifically, cancer patients with prescriptions had a significantly lower score in each summary score of the SF-12, and a significantly higher score in the K-6 and the PHQ-2 than age-matched non-cancer population.

The associations between patient characteristics variables and the HRQoL were mostly aligned with literature. Better HRQoL was reported by patients who were younger [52, 63] and with higher education.[55, 56, 63, 69] The effect of age on worse physical health could be partially explained by the fact that about 78% of all cancers are diagnosed in persons with 55 years and older.[4] In addition, cancer patients with chronic diseases have a worse physical health,[52, 60] and Hispanics were more likely to report worse mental problems than non-Hispanics.

Secondly, this study calculated the expenditures for prescribed medications associated with cancer. After controlling for different confounding factors, the predicted annual mean total and out-of-pocket expenditures associated with cancer medications were $2,572.1 and $597.1, respectively. Both the medical and policy communities increasingly concern the burden of out-of-pocket expenses on cancer patients. This analysis also examined how certain demographic and socioeconomic characteristics are strongly associated with high financial burdens. There is a lack of studies which has examined the prescription expenditures associated with cancer among groups of different demographic and socioeconomic characteristics. Yet the current study findings mirror general trends reported in the literature. This multivariate analysis revealed that patient characteristics such as age, region, insurance status, chronic conditions and HRQoL had significant impact on cancer prescription drug expenditures.

Total and out-of-pocket expenditures significantly increased with age. Elderly cancer patients had a higher level of spending on cancer prescription medications than nonelderly, especially those in the age category of 18 - 39. This result mirrors general trends reported in the literature.[76, 77, 78, 79, 80, 86] Similar to the results obtained by Ezzati et al.[77] and McKercher et al.[79], there were large differences of total and out-of-pocket expenditure between elderly and nonelderly patients.

Previous studies have consistently found that male paid less for their prescription medications expense than female.[77, 80, 81, 86] However, in current analysis this difference was not evident. Hence the hypothesis 2 was not supported.

With regard to race/ethnicity, this study found that whites had higher total and out-of-pocket spending than blacks. Although Hispanics spent higher total and out-of-pocket expenditures than non-Hispanics, these differences were not significant. Nevertheless whites actually incurred higher expenditures, which is similar to previous literature findings.[77] Therefore, the hypothesis 3 was supported.

Among the socioeconomic status, it was shown that patients living in the West or MSA predict a lower prescription spending than patients living in other regions.[77, 86] In this study, out-of-pocket expenditures for patients living in the Northeast were 105.44% higher than patients living in the West, while patients living in MSA paid 17.3% lower out-of-pocket expenditures than patients living in non-MSA. However, MSA is not a significant factor.

With respect to hypothesis 4 - "Patients with lower SES (classified as poor or having low income, uninsured) experience greater total/out-of-pocket expenditures associated with prescription cancer medications in comparison to their corresponding counterparts." The finding of effect of income level did not support it.

In terms of income levels, this study revealed that patients with poor or low family income had lower total and out-of-pocket prescription cancer spending than those who were with high family income ($p < 0.05$). Only patients with low personal income had higher total prescription expenditure than those with high personal income.

When considering prescription medication expenditures, clarifying the influence of patients' health insurance status is important for making a health policy. In this study, persons covered by Medicare insurance paid higher total and out-of-pocket money for prescription medicine in compared with other insurance groups. Similar to the results from Stagnitti et al.,[89] Medicare beneficiaries spent much higher average expense than those in the non-Medicare population, and uninsured had the lowest average annual total expense. Patients enrolled under Medicaid or uninsured patients paid less for their medicines by out-of-pocket compared with their counterparts. This difference gives the researchers and policy makers an alarm to pay attention to those vulnerable people regarding their access to health care.

In addition, this study also revealed that patients who were current smokers incurred less total and out-of-pocket expenditures for prescription medication than those who were former smokers. Patients experienced high blood pressure, high cholesterol, joint pain or arthritis had higher predicted mean total and out-of-pocket expenditures than patients not experienced these chronic conditions.

Furthermore, this study tried to associate HRQoL scores and medical expenditures. Previous literature reported that poor HRQoL was associated with higher prescription expenditures.[77, 90, 93, 94] The hypothesis in this study to be tested was whether cancer patients with lower physical or mental SF-12 scores, higher K-6 or PHQ-2 scores are more likely to accrue higher prescription medicine expenditures. The present study findings provide the evidence that higher out-of-pocket medicine expenditures incurred by patients with worse physical health or more serious depression. However, patients with better mental health also had higher out-of-pocket medicine spending. One explanation maybe that patients' mental health was greatly improved by these medications. The other explanation was that the information of HRQoL measured by these instruments is not obtained at a regular interval after taking cancer medications.

2.6.2 Study Strengths and Limitations

This study used the latest public use data drawn from the year 2008 Medical Expenditures Panel Survey (MEPS) for research. The MEPS is an annually nationally representative survey of the civilian non-institutionalized population in the U.S. Due to the secondary use of a pre-existing data, all independent and dependent variables were not exclusively designed for the objectives of this study. Detecting the time sequence of cancer patients taking prescription medications is difficult. An alternative method is to review medical-chart individually. However, performing this kind of study is very costly and time-consuming compared with using secondary data. In this section the discussions include the strengths and limitations of using secondary administrative dataset in this study.

Study Strength

Firstly, MEPS data has high accuracy and reliability. The MEPS is an annual set of large-scale surveys on the utilization of health care, insurance coverage, expenditures and payment sources for the U.S. civilian non-institutionalized population. It has a high-level agreement with physicians, and allows researchers to identify the disease by ICD-9-CM codes rather than from the answers to questions. Furthermore, MEPS collects information from pharmacy providers frequented by the survey respondents, and it takes measures to address the underreporting issues by relieving the household of the report.[111] Hence, the accurate and detailed information on medications could be helpful for deeply understanding the factors affecting cancer patients' quality of life and expenditures.

Secondly, MEPS survey improves the validity and breadth of self-reported response. The response rate for the 2008 Self-Administered Questionnaire (SAQ) is relatively high, which is 92.7%.[104] All the HRQoL measures in SAQ – the SF-12v2, the K-6 for general psychological distress and the PHQ-2 for depression, are proved to be valid and reliable. To my knowledge, this study is the first study to examine cancer patients' health status by using of these three different instruments. This study conducts a comprehensive comparison of patient-reported health status between the cancer and non-cancer populations and provides important information on the impact of cancer risk factor clusters on HRQoL.

Thirdly, the literature which has examined cancer patients treated with prescription medications by using nationally representative database such as MEPS are lacking and mostly outdated. This study uses year 2008 MEPS data, which is by the time the latest and most complete dataset available from MEPS website. Furthermore, to my knowledge, this study is also the first attempt to assess costs and health status associated with cancer patients taking prescription medications by using a nationally representative database. HRQoL assessment could provide information that is not available from diagnoses or other health record information resources. Meanwhile, it also reveals the patients' thoughts about the efficacy of treatment, which may influence their utilization of medical services. In the models of predicting medical expenditures, relatively few studies have used self-reported health status as a variable.

Fleishman et al.[126] used a nationally representative sample to estimate predictive models that included the SF-12 health status measure, and pointed out that the SF-12 summary scores were significantly associated with expenditures, after controlling for demographic characteristics and specific chronic conditions. In the current study, lower physical SF-12 scores and higher depression (PHQ-2) scores were significantly associated with higher prescription medication expenditures.

Study Limitations

Generally, administrative datasets are likely to cause potential errors in data collection, editing, or difficulty in evaluation of imputation. This study used administrative dataset. Without doubt, this leads to some limitations.

Firstly, a main limitation of this study is the observational design. Self-report does not provide a gold standard; it may potentially bias the results. In addition, because the data are cross-sectional, the causal relationship between medication therapy and HRQoL cannot be determined. However, the findings of this study provide an estimate of the potential impact of prescription medications on HRQoL of cancer adult patients.

Secondly, MEPS does not include certain measures that are more responsive to HRQoL among patients with cancer (e.g., the functional assessment of cancer therapy-General (FACT-G)). The SF-12, K-6 and PHQ-2 are generic instruments which could be used to assess outcomes across many medical conditions, as well as with healthy population. They are less sensitive and responsive to the changes when assessing quality of life in specific patient groups.

Thirdly, the estimates obtained in this study do not represent the HRQoL and prescription expenditures of all cancer patients in the U.S. because the study population excludes institutionalized population. In addition, the expenditures used in this study included only the spending for prescription medications, while many cancer patients are more likely to have expenditures of hospital inpatient stay, emergency room visits and other medical services. Moreover, the total number of cancer patients sampled may be comparatively small in MEPS, since MEPS is not designed to

provide statistically robust, population-based information on health status by types of cancer.[43] Hence, the small sample size of this study will influence its representation of national estimates.

2.6.3 Health Policy Implication

Based on the findings, there are a few suggestions for the implication of health policy. First of all, this study provides additional empirical evidence to demonstrate socio-demographic differences assessed by HRQoL measures. Healthcare researchers and clinicians need to be aware that persons between 18-39 years of age, unmarried, Hispanics, not living in city area, less education attainment or currently smoking had greater tendency towards physiologic distress or depression. There is a need to emphasize screening physiologic problem in cancer patients taking with prescription medications, because such problems could cause adverse effects and increase health care costs.

Moreover, this study is designed to document how the patient characteristics affect cancer prescription medication expenditures among adult cancer patients. It helps establish a framework for understanding the real cancer-related medication spending among cancer patients and gives a comprehensive and up-to-date understanding of cancer medication treatment and expenditures to assist manage medical costs.

The MEPS data include a crucial component of health expenditures - health insurance coverage. It is necessary to examine the relationship between health insurance status and out-of-pocket expenditures among vulnerable patients with prescription medications. Vulnerable patients are elderly, female, blacks, Hispanics, uninsured, or with low income. They particularly have the restrictions of insurance coverage and access to health service utilization, including prescription medications. Hence, health policy makers should develop more specific interventions to help these disadvantaged people.

2.6.4 Suggestions for Future Studies

Since the study has some limitations, there are some suggestions for future research. Firstly, the current study had a cross-sectional design, that's why it is not possible to determine causal relationships of socio-demographics against HRQoL or socio-demographics against prescription expenditures. Further longitudinal studies will be required to test the presence of associations and fully interpret their clinical significance.

Additionally, the findings of this study did not support the following hypothesis – "female patients or patients classified as poor or having low income experience greater total/out-of-pocket expenditures associated with prescription cancer medications in comparison to their counterparts". In this study, the impact of gender was not evident. And it was found that patients with poor or low family income had lower total and out-of-pocket prescription spending than those who were with high family income. The differences indicated that cancer patients with higher income had higher level of expenditures, which contradicted the hypothesis. Thus, further studies are needed to examine such differences.

Finally, a full estimation of the economic burden of cancer prescription medications should also include the indirect costs, which have important economic value as well. Morbidity cost of illness is the most common indirect cost. It is related to the lost or impaired ability to work or reduced productivity due to illness (e.g., days lost from work, foregone wages), as well as the economic output and the time lost or forgone by the patients' family and friends from usual activities (e.g., income lost by family members, restricted leisure time).[38] In addition, mortality costs as part of indirect costs and intangible costs are also of considerable interest to policymakers. Since this study only focused on direct prescription expenditures of treating cancer, overall predicted expenditure associated with cancer was underreported. A simple descriptive analysis about the lost productivity was performed in this study. However, a more detailed analysis is needed to capture both direct and indirect expenditures associated with lost productivity, premature mortality, or pain and suffering, which

will provide a more precise overall predicted prescription medication expenditure for cancer.

2.6.5 Conclusion

This study comprehensively examined the patient characteristics related to HRQoL and expenditures on prescription cancer medications among adult cancer patients by using the latest and most complete MEPS dataset. The results revealed that cancer population with prescription medications had impaired HRQoL and lost more productivity compared with age-matched non-cancer population. It also indicated that the disparities existed among HRQoL and prescription cancer expenditures. Specifically, older age, Hispanics, less education attainment and chronic conditions were risk factors for HRQoL. Differences existed in the total and out-of-pocket cancer prescription spending between elderly and nonelderly, black and white population, living in the West and living in the other regions. Insurance status, smoking status and chronic conditions also had significant impact. Moreover, patients with worse physical health or greater tendency towards depression were more likely to incur higher prescription medication expenditures. Findings from this study might assist health professionals to pay more attention to primary cancer care from the patient's perspective. Further research is needed to determine causal relationships to test the associations between the demographics/SES and the HRQoL/prescription medication expenditures by longitudinal studies. Additionally, a more detailed analysis is needed to capture both direct and indirect costs to provide more precise overall predicted prescription medication expenditures for cancer.

Chapter 3: Patient Satisfaction and Subjective Experiences of Treatment with Breast Cancer Hormonal Medications

3.1 Abstract

Objective: To examine patient satisfaction and subjective experiences of breast cancer treatment with hormonal medications – tamoxifen and Aromatase Inhibitors (AIs), by using patient self-reported data.

Methods: The data used for this study were collected from the website www.askapatient.com, which invites patients to rate their medications and comment on their drug experience. 1,121 female breast cancer patients with age of 40 and above taking hormonal medications were extracted. Multivariate analyses were used to compare side effects, and evaluate both individual and condition characteristics that affect satisfaction with hormonal medications among breast cancer patients.

Results: Patients receiving AIs experienced significantly more arthralgia/myalgia, bone events, carpal tunnel syndrome, vaginal dryness, sexual dysfunction and sleep disorders, while patients receiving tamoxifen experienced significantly more hot flashes, night sweats, vaginal discharge/bleeding and other serious gynecologic side effects. Side effects, especially musculoskeletal symptoms and nervous system problems, significantly and negatively affected patient satisfaction with hormonal medications. Long-term medication treatment and currently consistent use of medications were also important determinants of medication satisfaction. In addition, anastrozole and letrozole patients had a higher probability of experiencing satisfaction than tamoxifen patients.

Conclusions: This self-reported-data study found that the majority of the patients on current hormonal medications incurred significant side effects, which negatively affected patient satisfaction. Additionally, long-term and currently consistent uses of medications were also important factors affecting patient satisfaction with medication.

3.2 Introduction

Study background, objectives, research questions and hypotheses will be presented in this section.

3.2.1 Background

According to year 2008 World Cancer Report, breast cancer is the most frequently diagnosed type of cancer among women. And today, after lung cancer, it is the second leading cause of cancer death in women.[2] Breast cancer is a cancer that starts in the breast. Usually, the tumor begins in the cell of the lobules that are the glands for milk-producing, in the cell of the ducts as well, which are the passages draining milk from the lobules to the nipple.[127] In the United States, breast cancer is the most commonly diagnosed cancer for women after skin cancer, accounting for nearly one in four cancer cases diagnosed in women.[128] Men are generally at low risk for developing breast cancer. Each year more than 190,000 new cases are diagnosed and cause more than 40,000 deaths.[129] The American Cancer Society (ACS) estimates that 192,370 new cases of invasive breast cancer would be diagnosed among women and approximately 40,170 would die of breast cancer in the U.S. in year 2010.[128] The most significant risk factors for developing breast cancer are age and gender (female). Incidence and death rates of breast cancer generally increase with age. According to the ACS, 95% of new cases and 97% of breast cancer deaths occurred in women aged 40 and older during year 2002 to 2006.[128]

Over the past few decades, the incidence of breast cancer has increased steadily in the United States, but breast cancer mortality has declined, indicating an increased survival rate. The predominant reason is the improved treatments. Generally, the choice of treatment depends on the stage of breast cancer, whether the tumor is positive for certain receptor, the overall health condition of the patient, as well as the risks and benefits associated with treatment. Conceptually, treatment options for breast cancer patients include local and systemic treatments. Local therapy treats a tumor at the site without affecting the rest of the body. In the case of metastatic disease, local treatment still could be applied to specific places where cancer might

have spread, such as bones or ovary. Surgery and radiation therapy are examples of local therapies. Systemic therapy is directed at the whole body. It uses anti-cancer drugs that are injected into the vein or taken orally. These drugs travel through the bloodstream and affect cells in all parts of the body.[128] Systemic therapy could be given to patients before or after surgery. It could also be used in treating metastasis breast cancer. In such conditions, complete surgical excision is not possible, and therefore systemic therapies are the main treatment option.[128] Systemic treatment includes chemotherapy, biologic therapy and hormonal therapy.

Approximately 75% of all breast cancers occur in postmenopausal women in Western countries, among which about 80% are hormone-receptor-positive.[130,131] Hormonal therapy, also called endocrine therapy or hormone therapy, is the best treatment choice for these breast cancer patients. It could be used in both early and advanced stages. Currently, the most widely used daily oral hormonal medications include tamoxifen and Aromatase Inhibitors (AIs) - anastrozole (Arimidex®), letrozole (Femara®) and exemestane (Aromasin®). Tamoxifen has been considered the standard hormonal treatment for premenopausal and postmenopausal breast cancer patients for decades, while AIs are the newest class of drugs, which can potentially be effective to postmenopausal women who become refractory or may become resistant to tamoxifen. All of these medications are approved by the U.S. Food and Drug Administration (FDA). The role of each hormonal therapy depends on woman's stage of disease, menopausal status, overall medical condition, and personal considerations. These medications are used to lower the risk of early-stage breast cancer recurrence after surgery, shrink or slow the growth of advanced-stage breast cancer, or lower the risk of patients who are at high risk but have not been diagnosed with breast cancer.

Although tamoxifen and AIs demonstrate a superior therapeutic efficacy in both early and advanced disease stages of postmenopausal women, they produce different toxic side effects. The most common side effects associated with tamoxifen are vasomotor symptoms, vaginal discharge, and vaginal itching or dryness.[129] Patients who receive AIs experience vaginal dryness, sexual dysfunction, arthralgia, cardiovascular disease, and bone disease such as decreased bone mineral density or fractures.[132] In addition, tamoxifen will cause some serious life-threatening side effects (i.e., thromboembolic and cerebrovascular events, endometrial cancer).[129]

These side effects deleteriously effect the patients' quality of life and influence drug compliance. Therefore, when considering the management of breast cancer hormonal medications, in addition to assess the impact of the medication on patients' health-related quality of life (HRQoL), it is also essential to assess patient satisfaction with that medication. Currently available quality of life (QoL) studies show that although the side effect profiles of tamoxifen and AIs vary significantly, there are no clinically important differences in overall QoL. Consequently, patient satisfaction is particular useful when differentiating these treatments.

Patient satisfaction with medication mainly evaluates the patient's experience after taking the medication.[26] It also reflects patients' treatment-related behaviours, such as correct use of the medication, the likelihood of continuing to use medication, and adherence with medication.[30] It is influenced by the outcomes of the treatment, especially HRQoL and symptom status. Evidence has also shown that in randomized controlled clinical trials for patients with chronic disease including cancer, satisfaction outcomes can be more sensitive to the changes than outcomes of quality of life.[133] Hence, medication satisfaction information is potentially useful for deeply understanding the cancer patients' perspective on their current treatment and can differentiate among alternative treatments. However, to date, there have been no empirical studies which systematically explore this topic on breast cancer hormonal medications.

3.2.2 Study Objectives

This study attempts to attribute treatment related toxicity and satisfaction with hormonal medications by using patient self-reported data. It is carried out to give a better understanding of the important issues in treatment decision making for postmenopausal women with breast cancer.

One objective of this study is to assess and compare the side effects reported by breast cancer patients with different hormonal medications. Monitoring of side effects after taking hormonal therapy is crucial in medical oncology practice, because it could be balanced against a minimal survival advantage to make the optimal choice of

treatment.[134] As known from several publications, physician-guided symptom assessment is not sufficient to give a full picture of the real side effects produced by hormonal treatments, it normally underestimates the real treatment burden.[134,135,136] Therefore, there is an increasing recognition of the importance of obtaining breast cancer patients' views about their problems and their treatments.

The other objective of this study is to examine patient satisfaction with the different hormonal medications. Tamoxifen and AIs have been demonstrated to have similar survival rates in postmenopausal patients,[137] but differ with respect to side effects. Nevertheless, there were no clinically important differences in overall QoL. Consequently, patient satisfaction is particular useful when comparing the benefits of these hormonal medications. This information can be served as the baseline for the policy makers on how to best improve breast cancer outcomes over time. Currently, the published literature on cancer treatment satisfaction has been scarce, without clear indication of whether breast cancer patients are indeed satisfied with their hormonal medications, and what their subjective experiences are.

The expected objective of this study is that by examining patient satisfaction and subjective experiences of treatment with breast cancer hormonal medications, the findings will provide a new benchmark for these values which can be applied to the management of breast cancer hormonal medications.

3.2.3 Research Questions and Hypotheses

This study is based on the patient self-reported data collected from an Internet website www.askapatient.com, which is a database providing patients' opinions and ratings of medicine effectiveness.[138] This database includes the FDA approved medications. It also includes patients' opinion polls on healthcare topics, and a section of health care research assistance.[138] The research questions and their hypotheses are described below.

Research Question one:

"What are the most common side effects reported by breast cancer patients after taking hormonal medications?"

The hypotheses to be tested are as follows:

1. Breast cancer patients taking tamoxifen reported more vasomotor symptoms and vaginal discharge/bleeding.
2. Breast cancer patients taking AIs reported more arthralgia/myalgia, carpal tunnel syndrome, vaginal dryness and bone events.

Research Question two:

"What are the factors associated with breast cancer patients' satisfaction after taking hormonal medications?"

The hypotheses to be tested are as follows:

1. The side effects have negative impact on patients' rating on satisfaction.
2. The duration of medication treatment is longer, the probability of being satisfied or the likelihood of rating a higher score is higher.
3. Patients who persist as current users of medication are more likely to rate a higher score on satisfaction.
4. Patients with concurrent drug use are more likely to rate a higher score on satisfaction.
5. AIs patients had a higher probability of experiencing satisfaction than tamoxifen patients.

3.3 Literature Review

This section will provide a systematically literature review related to this study. The topics include an overview of the quality of life (QoL) research on breast cancer hormonal medications. QoL research including disease-related symptoms, toxic effects of therapy, emotional, socioeconomic and functional effects of living, could affect the

patients' experience with treatment. In addition, a comprehensive review on patient satisfaction with medication is provided.

3.3.1 Quality of Life (QoL) Studies on Breast Cancer Hormonal Medications

A comprehensive literature search in PubMed was conducted to identify English-language studies assessing quality of life (QoL) in breast cancer patients with hormonal therapy. Publications through year 2010 were searched for. The key words "breast neoplasms", "tamoxifen", "anastrozole", "letrozole", "exemestane", "quality of life" and "outcome assessment" were included in the search. After scanning titles and abstracts, studies that appeared to be relevant were reviewed in detail. Additionally, reference lists of selected papers were used to find articles that did not appear in the primary search.

QoL Studies of Tamoxifen

The effects of tamoxifen on QoL are collected from two randomized trials: the Wisconsin Tamoxifen Trial and the National Surgical Adjuvant Breast and Bowel Project P1 (NSABP-P1) Trial. See Table 16.

Table 16: Randomized Trials Evaluating QoL of Tamoxifen

Trial	Timing	Intervention	Size	Instrument	Outcomes
Wisconsin (postmenopausal)					
Love et al. 1991 [139]	post surgery	Placebo × 2y Tamoxifen × 2y	140	Symptom questionnaires	No difference in overall QoL; Vasomotor and gynecologic symptoms↑ with tamxifen
NSABP-P1 (premenopausal and postmenopausal)					
Day R et al. 1999 [140]	prevention	Placebo × 5y Tamoxifen × 5y	11064	CES-D, SF-36, sexual functioning scale, SCL	No difference in overall QoL; Vasomotor, gynecologic symptoms and sexual dysfunction ↑ with tamoxifen
Day R et al. 2001 [141]	prevention	Placebo × 5y Tamoxifen × 5y	11064	CES-D	No difference

Notes:

NSABP: National Surgical Breast and Bowel Project; CES-D: Center for Epidemiological Studies-Depression Scale; SF-36: Medical Outcomes Study 36-Item Short Form Health Status Survey; SCL: Symptom Check List.

↑ means "increase", ↓ means "decrease".

Wisconsin Tamoxifen Trial is a randomized, double-blind, placebo-controlled trial which included 140 postmenopausal women with axillary node negative breast cancer.[139] Patients were randomly assigned to receive tamoxifen or placebo. Data on symptoms and overall QoL were collected over 24 months by symptom questionnaires. Women receiving tamoxifen had increased hot flashes (tamoxifen 67.2% vs. placebo 45.4% at 6 months, $p < 0.01$). Gynecologic symptoms (one or more of the following: vaginal discharge, irritation, or bleeding) were also more common (29.7% vs. 15.1% at 6 months; $p < 0.05$) in tamoxifen users. No differences were detected with regard to QoL, bone pain, joint pain, nausea, difficulty sleeping, irritability, depression, fatigue, or heartburn.

The National Surgical Adjuvant Breast and Bowel Project P1 (NSABP-P1) Trial recruited 11,064 women who were randomized to receive tamoxifen or placebo with 36 months follow-up period.[140] HRQoL assessment was performed by the Center for Epidemiological Studies-Depression Scale (CES-D), the Medical Outcomes Study (MOS) 36-item Short Form Health Survey (SF-36), the MOS sexual functioning scale, and a Symptom Check List (SCL). No differences were found between tamoxifen and placebo for CES-D and SF-36. Tamoxifen use was associated with an increase in vasomotor symptoms, gynecologic symptoms and sexual functioning problems.

A sub-study of NSABP-P1 used CES-D to examine the psychological effects of tamoxifen for breast cancer patients.[141] CES-D scores of 16 or higher indicated affective distress. This study showed no difference in the women who scored 16 or higher of tamoxifen and placebo.

All the above studies found no differences in QoL between tamoxifen and placebo, despite that significant increase in vasomotor and gynecologic symptoms with tamoxifen was observed.

QoL Studies of Aromatase Inhibitors (AIs)

Aromatase Inhibitors (AIs) in postmenopausal women have successfully increased survival rates and disease-free survival rates. However, treatment with AIs seems to

produce a lot of side effects. The most common short-term adverse events include hot flashes, fatigue, arthralgia, muscle pain, and increases in osteoporosis.[132] Up to now, quite a number of randomized trials about AIs are implemented; however the studies of QoL evaluation are limited.

Eight studies about randomized trials evaluating QoL of AIs with tamoxifen have been identified, including the Arimidex, Tamoxifen, Alone or in Combination trial (ATAC), the Intergroup Exemestane Study (IES), the National Surgical Adjuvant Study of Breast Cancer (NSAS BC), the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial, and the National Cancer Institute of Canada Trial (MA.17). Another two QoL studies were carried out with regard to head-to-head comparing anatrozole with letrozole. One was about adjuvant treatment, and the other was about metastatic treatment. See Table 17.

QoL studies of the Arimidex, Tamoxifen, Alone or in Combination trial (ATAC) were reported for two and five years follow-up. In the ATAC QoL sub-protocol over a period of two years, 1,021 of 9,366 patients were randomized to receive anastrozole, tamoxifen, or a combination.[142] The Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) with an additional Endocrine Subscale (ES) questionnaire was used. The primary endpoint was the Trial Outcome Index (TOI) of the FACT-B. It is the summary scores from the Physical Well-Being (PWB), Functional Well-Being (FWB) and the breast cancer subscales.[138] Secondary endpoints were the total ES score and the Emotional Well-Being (EWB) and Social Well-Being (SWB) subscales of the FACT-B. In this sub-study, response rates were approximately 85% for all time points. Overall QoL improved over time, and no significant differences between groups in TOI scores, ES, EWB or SWB scores were observed. Endocrine symptoms increased between baseline and three months for all groups and stabilized or improved slightly thereafter. Compared with sole tamoxifen users, anastrozole users only reported significantly fewer frequencies of cold sweats, but the same occurrence of hot flashes. Vaginal discharge was reported less often by patient receiving anastrozole. Conversely, vaginal dryness, painful intercourse and loss of libido were significant more common on anastrozole. There were no significant differences of neuropsychological, gastrointestinal symptoms and related symptoms in all treatment groups.

Table 17: Randomized Trials Evaluating QoL of Aromatase Inhibitors

Trial	Timing	Intervention	Size	Instrument	Endpoints	Outcomes
ATAC						
Fallowfield L et al.2004 [142]	Post-surgery or chemotherapy	Anastrozole × 5y Tamoxifen × 5y Combination × 5y	1021	FACT-B+ES	Primary: TOI Secondary: total ES score, EWB and SWB subscales of the FACT-B	No difference in overall QoL or the endocrine subscale
Cella D et al.2006 [143]	Post-surgery or chemotherapy	Anastrozole × 5y Tamoxifen × 5y	1105	FACT-B+ES	Primary: TOI Secondary: ES score, EWB and SWB subscales of the FACT-B	No difference in overall QoL or the endocrine subscale
IES						
Fallowfield L et al.2006 [144]	Following tamoxifen × 2-3y	Exemestane × 2-3y Tamoxifen × 2-3y	582	FACT-B+ES	Primary: TOI Secondary: total FACT-B + ES score, ES score	No difference in overall QoL or the endocrine subscale
NSAS BC 03						
Ohsumi S et al. 2010 [145]	Post-surgery and Following tamoxifen × 1-4y	Anastrozole × 5y Tamoxifen × 5y	706	FACT-B+ES; CES-D	Primary: DFS, adverse events Secondary: HRQoL, psychological distress	Better QoL in tamoxfien group; hot flashes and vaginal discharge with anastrozle ↑; dizziness, diarrhea and headache with tamoxifen ↑
NSAS BC 04 (sub-study of TEAM)						
Takei H et al. 2006 [146]	N/A	Anastrozole × 5y Exemestane × 5y Tamoxifen × 5y	247	FACT-B+ES; CES-D	Primary: Adverse events Secondary: HRQoL	No difference in overall QoL, endocrine subscale, or psychological distress
DUTCH TEAM TRIAL						
van Nes JGH et al .2009 [147]	Following tamoxifen × 2-3y	Exemestane Tamoxifen	742	EORTC QLQ-C30, EORTC QLQ-BR 23, FACT-ES	Not specified	No difference in overall QoL; insomnia ↑, sexual functioning ↓ with exemestane
MA-17						
Whelan TJ et al.2005 [148]	Letrozole Following tamoxifen × 5y	Letrozole × 5y Placebo × 5y	3612	SF-36; MENQOL	Not specified	No difference in overall QoL; small differences in bodily pain and vasomotor symptoms
Muss B et al. 2008 [149]	Letrozole Following tamoxifen × 5y	Letrozole × 5y Placebo × 5y	5169	SF-36; MENQOL	Not specified	No difference in overall QoL among letrozole- and placebo-treated patients age ≥ 70 years
ALIQUIT						
Dixon JM et al. 2010 [150]	N/A	Letrozole to Anastrzole × 3m Anastrozle to Letrozole × 3m	181	FACT-B+ES	QoL, toxicity, patient preference	No difference in overall QoL
Advanced Breast Cancer						
Thomas R 2003 [151]	Following tamoxifen	Anastrozole × 1m Letrozole × 1m	72	FACT-B+ES	QoL, toxicity, patient preference	Overall QoL ↑ with letrozole; lethargy, joint pain, nausea, hot falshes, abdominal discomfort ↓ with letrozole

Notes:

QoL: Quality of Life; ATAC:Arimidex,Tamoxifen,Alone, or in Combination; IES: Intergroup Exemestane Study; NSAS BC: National Surgical Adjuvant in Study of Breast Cancer; FACT-B: FunctionalAssessment of Cancer Therapy-Breast; ES: Endocrine Subscale; SF-36: Medical Outcomes Study 36-Item Short Form Health Status Survey; MENQOL: Menopause SpecificQuality of Life Instrument; CES-D: Center for Epidemiologic Studies Depression scale; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; BR: Breast; ALIQUIT: Anastrozole vs. Letrozole, an Investigation of Quality Of Life and Tolerability; TOI: Trial Outcome Index; ES:Endocrine Subscale; EWB: Emotional Well-Being; SWB: Social Well-Being.

↑ means "increase", ↓ means "decrease".

Cella D et al.[143] studied HRQoL of 1,105 patients over the full five-year adjuvant treatment period. The findings were consistent with the results from the two-year follow-up analysis. No statistically significant differences were noted in the TOI scores between treatments at five years, and the mean TOI scores showed continued slight improvement in both the treatment groups from two years to five years. Statistically, total ES, SWB or EWB scores were not significantly different between treatment groups. However, differences in patient-reported side effects existed: compared to tamoxifen, anastrozole was associated with significantly more occurrences of diarrhea (anastrozole 3.1% vs. tamoxifen 1.3%), vaginal dryness (18.5% vs. 9.1%), decreased libido (34.0% vs. 26.1%), and dyspareunia (17.3% vs. 8.1%), while significantly less occurrences of dizziness (anastrozole 3.1% vs. tamoxifen 5.4%) and vaginal discharge (1.2% vs. 5.2%).

The Intergroup Exemestane Study (IES) trial recruited 582 of 4,742 women to a QoL sub-study with 24 months of follow-up. [144] Both the FACT-B and ES questionnaires were used. The primary endpoint was the TOI. Secondary endpoints included the total ES score and individual endocrine symptoms. In this study, response rates were 85% for all time points. The overall QoL (measured by TOI and total FACT-B+ES), and total ES change scores were noted not statistically different, but endocrine symptoms, especially vasomotor symptoms, improved over time. Hot flashes (46% vs. 45% for exemestane and tamoxifen respectively) decreased over time in both groups. Except for vaginal discharge was reported less frequently in exemestane group ($p < 0.001$), between the groups there were no significant differences for any other gynecologic symptoms, neuropsychological or gastrointestinal symptoms.

In the National Surgical Adjuvant in Study of Breast Cancer (NSAS BC 03) trial, postmenopausal breast cancer patients were with a slightly better HRQoL with further tamoxifen treatment after adjuvant tamoxifen compared with those switching to anastrozole.[145] In this trial, 706 patients who had been on adjuvant tamoxifen for one to four years without recurrence were randomized to either five years of anastrozole or an additional five years of tamoxifen. Patients were asked to complete FACT-B and ES questionnaires, and Center for Epidemiologic Studies Depression scale (CES-D) at baseline, three months, one and two years. The tamoxifen group reported statistically significantly better total scores of FACT-G, FACT-ES and the scores of Physical

Well-Being (PWB) subscale than the anastrozole group. Total FACT-B scores were marginally better in the tamoxifen group. There were no statistically significant differences between the two treatment groups for the scores of CES-D, or the scores of the endocrine symptom subscale of FACT-ES. However, some items in the endocrine symptoms showed statistically significant differences. Hot flashes and vaginal discharge were worse in the tamoxifen group than in the anastrozole group, while dizziness, diarrhea and headache were worse in the anastrozle group than in the tamoxifen group.

The NSAS BC 04 trial compared the effects of five-year exemestane, anstrozole and tamoxifen on HRQoL and psychological distress in Japanese postmenopausal women with hormone responsive early-stage breast cancer after receiving adjuvant therapy.[146] Patients were asked to complete FACT-B, FACT-ES and psychological distress (CES-D) at baseline, 3 months, and 1 year after the randomization. There were no significant differences for any of the scales used to assess QoL among the three treatment groups. The mean scores of all the patients increased significantly over the period in FACT-G total, FACT-B total, and breast cancer subscale of FACT-B ($P \leq 0.01$ for all), whereas the mean scores of all the patients became significantly worse in the endocrine subscale of FACT-ES ($P = 0.04$) but did not change in CES-D.

The Dutch Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial included 2,754 patients, in which 742 patients were invited onto the QoL sub-protocol.[147] Patients were asked to fill in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EROTC QLQ-C30), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer (EORTC BR 23), and FACT-ES. After one and two years of hormonal treatment, there were no significant differences in global health status/QoL between treatments. Exemestane use was associated with significantly more insomnia and worse sexual functional problems than tamoxifen use. There were no significant differences in physical functioning, role functioning, cognitive or emotional functioning and endocrine symptoms between the two treatment groups.

The National Cancer Institute of Canada Trial (MA.17) assigned 3,612 of 5,187 women to the QoL sub-study with the median follow-up of 30 months.[148] The Medical

Outcomes Study 36-item Short Form Health Survey (SF-36) and the Menopause Specific Quality of Life (MENQOL) questionnaire were completed at baseline, six-month and annually. The primary and secondary endpoints were not specified. The SF-36 summarized subscales into two global scores: the physical and mental component summary scores (PCS and MCS). MENQOL summarized subscales into four domains: vasomotor, physical, psychosocial and sexual. In the sub-study, compliance with the QoL assessment was over 90% for all time points. No significant differences were seen between letrozole and placebo arms in mean change scores from baseline for SF-36 PCS and MCS scores. Small but statistically significant differences were detected on physical functioning, bodily pain and vitality scales of SF-36 domains, and MENQOL sexual and vasomotor domains. In the response analysis, a significant difference was noted for the bodily pain domain (percentage of patients reporting worse QoL, placebo 47% vs. letrozole 51%; p = 0.009) and the vasomotor domain (22% vs. 29%; p = 0.001). On the symptom analysis, letrozole use resulted in a significant increase in hot flashes (placebo 17% vs. letrozole 22%; p = 0.0002) and sweating (14% vs.18%, p = 0.003). An increase in muscle and joint aches, vaginal dryness, night sweats, and sleeping difficulty in the letrozole group was observed. There were no differences in sexual desire, avoiding intimacy, poor memory, depression or weight gain. Although a small number of patients suffered from adverse effects, no major impact of letrozole therapy was seen on overall QoL.

Muss B et al.[149] studied the QoL in early-stage breast cancer older women treated with letrozole or placebo after five years of tamoxifen. In this study, patients were divided into three age groups: younger than 60 years, 60 to 69 years, and age 70 years and older. The SF-36 and the MENQOL questionnaire were used to measure QoL. Compared with placebo receivers, patients receiving letrozole treatment showed only a modest decrease of QoL. In the oldest group (age 70 years and older), patients receiving letrozole had significantly worse QoL than those receiving placebo on the vitality, bodily pain, and physical scale at 6 months, and MENQOL vasomotor domain at 12 months. At 24 months, only a mild increase of MENQOL vasomotor symptoms was noted for the age group – age 70 years and older (p = 0.02), while it became similar to placebo at 36 months.

Anastrozole vs. Letrozole, an Investigation of Quality Of Life and Tolerability (ALIQUOT) study was an open-label crossover study of postmenopausal women with breast cancer receiving adjuvant AI therapy.[150] Patients were randomized to receive either three months of letrozole followed by three months of anastrozole or three months of anastrozole followed by three months of letrozole. QoL was assessed by FACT-B and FACT-ES. At the end of the six months study period, there was no significant change in overall QoL score or endocrine symptoms subscale score between anastrozole and letrozole. No differences in side effects were seen between the two drugs and patients receiving these two drugs had similar preference.

A multicenter, randomized, single-blind study compared QoL of metastatic breast cancer patients receiving anastrozole and those resceiving letrozole by the FACT-ES questionnaire.[151] After four-week follow-up, patients receiving letrozole showed a significant improvement compared with anastrozole in overall QoL scores. The sub score of endocrine symptoms and additional concerns (including hair loss, weight change, sexual attractiveness and self-awareness) also showed significant improvement for letrozole treatment. Furthermore, letrozole showed better tolerability than anastrozole. Letrozole induced less lethargy (letrozole 8% vs. anastrozole 19%), nausea (10% vs. 22%), joint pain (3% vs. 11%), abdominal discomfort (3% vs. 11%), appetite (2% vs. 14%) and headache (5% vs. 14%). And more than twice as many patients preferred to continue with letrozole therapy than with anastrozole at the end of the trial (letrozole 68% vs. anastrozole 32%).

In general, clinical trials of AIs have failed to show a significant deterioration in QoL for patients on AIs compared with tamoxifen or placebo. The head-to-head QoL comparison of AIs showed that letrozole provides better QoL than anastrozole for patients with metastatic breast cancer.

Other QoL Studies Focusing on Side Effects

Besides those randomized trials mentioned above, there are some studies focusing on the side effects reported by the patients receiving hormonal therapies, such as menopausal symptoms, cognitive functioning, etc. See Table 18.

Table 18: Other QoL Studies Focusing on Side Effects

Author	Timing	Intervention	Size	Instrument	Primary endpoint	Outcomes
Early-stage Brease Cancer						
Asmar L et al. 2004 [152]	Post-surgery or chemotherapy	Exemestane Tamoxifen	997	Symptom checklist	Menopausal symptoms	Vaginal dryness and bone/muscle aches with exemestane ↑
Francini G et al. 2006 [153]	Following tamoxifen × 2y	Exemestane Tamoxifen	60	EORTC QLQ-C30	Body composition, lipid profiles	No difference in overall QoL;fat mass, triglycerides, high-density lipoprotein cholesterol ↓with exemestane; FFM/FM ratio,low-density lipoprotein cholesterol ↑ with exemestane
Jones SE et al. 2007 [154]	Following tamoxifen × 2-3y	Exemestane Tamoxifen	1614	self-report menopausal symptoms questionnaire	Menopausal symptoms	Vaginal dryness, bone/muscle aches, difficulty sleeping↑ with exemestane; vaginal discharge, hot flashes ↓with exemestane
Schilder CM et al. 2009 [155]	Following A/C	Exemestane Tamoxifen Controls	128	FACT-B+ES, EORTC QLQ-C30, HSCL, CFQ, MFI-20	Neuropsychological functioning	No statistically significant differences of cognitive testing.
Schilder CM et al. 2010 [156]	Following tamoxifen × 2-3y	Exemestane Tamoxifen Controls	299	FACT-B+ES, EORTC QLQ-C30, HSCL	Cognitive functioning	Verbal memory and executive functioning ↓with tamoxifen.
Thomas R et al. 2008 [157]	Following tamoxifen × 3m	Exemestane Letrozole	184	FACT-B+ES, HFD, MRS,patient preference questionnaire, Arthralgia grading system	Hot flashes score	QoL ↑; hot flashes, mood, arthralgia↑ with AI.
Mamounas EP et al.2008 [158]	Following tamoxifen × 5y	Exemestane Placebo	454	MENQOL	Menopausal symptoms	No statistically significant differences in MENQOL.
Boehm DU et al. 2009 [159]	Following tamoxifen	N/A	136	50-item self-administered questionnaire	Side effects and level of influence on the physical, emotional and social functioning caused by tamoxifen	QoL ↓
Crew KD et al. 2007 [160]	Following a AI × > 3m	Anastrozole Letrozole Exemestane	200	self-administered questionnaire	Joint symptoms	More that 45% patients having AI-related joint pain and stiffness.
Henry NL et al. 2008 [161]	Following a AI × > 6m	Letrozole Exemestane	100	HAQ, VAS	Musculoskeletal symptoms	45.4% patients met criteria for rheumatologic referral; referred patients had higher HAQ and VAS scores
Ruhstaller T et al. 2009 [134]	Following hormonal therapy	Adjuvant Metastatic	373	C-PET	Symptoms of hormonal therapy	Hot flashes/sweats, low energy, fluid retention, vaginal dryness↑ with this study than in pivotal trials
Ochayon L et al. 2010 [162]	Following hormonal therapy	N/A	132	FACT-B+ES sociodemographic and medical information questionnaire	QoL, symptoms of hormonal therapy	Adjuvant hormonal therapy did not affect the QoL; A reduced number of symptoms indicarted a higher QoL; mood swings and irritability had a negaive impact on QoL
Advanced Breast Cancer						
Mouridsen H et al. 2004 [163]	Following a AI	Letrozole Tamoxifen	907	KPS scale	Not specified	Time to worsening of at least 20 points in KPS was significantly longer in letrozole group; more tamoxifen patients with mainly lung metastasese experienced worsening KPS scores by at least 20 points

Notes:

C-PET: Checklist for Oatients with Endocrines Therapy; A/C: Doxorubicin/Cyclophosphamide; CFQ: Cognitive Failures Questionnaire; HSCL: Hopkins Symptom Checklist-25; MFI-20: Multidimensional Fatigue Inventory; BCPT: Breast Cancer Prevention Trial; HFD: Hot Flushes Diary ; MRS: Mood Rating Scale; HAQ: Health Assessment Questionnaire; VAS: Visual Analog Scale; KPS: Karnofsky Performance Status; FFM/FM: Fat-Free Mass/Fat Mass.

↑ means "increase", ↓ means "decrease".

Asmar L et al.[152] used a 10-menopausal-symptom questionnaire to compare menopausal symptoms during the first year in 997 postmenopausal women who were randomized to tamoxifen or exemestane. Results showed that vaginal discharge ($p < 0.001$) was more common with tamoxifen, but vaginal dryness ($p = 0.0021$) and bone or muscle aches ($p < 0.001$) were more common with exemestane. With respect to vaginal bleeding, mood alteration, impaired word finding, low energy, difficulty sleeping and hot flashes, the differences of between-groups were noted not significant.

Francini et al.[153] examined the changes in body composition and lipid profiles in postmenopausal women who switched from tamoxifen to exemestane. EROTC QLQ-C30 was used to assess HRQoL. This randomized study reported that compared with baseline, exemestane group had improved global QoL scores, global health status and physical functioning, but there were no statistically significant between-group differences. In the exemestane group, fat mass had significantly decreased and the FFM/FM (Fat-Free Mass/Fat Mass) ratio had significantly increased, but not in the tamoxifen group; the differences were statistically significant. At the end of the one-year study period, triglycerides and high-density lipoprotein cholesterol significantly decreased, and low-density lipoprotein cholesterol significantly increased in the exemestane group.

There were three studies based on Tamoxifen Exemestane Adjuvant Multicenter (TEAM) Trial. One was menopausal sub-study, and the other two were cognitive sub-studies.

Jones et al.[154] investigated menopausal symptoms of breast cancer patients randomized to adjuvant tamoxifen or exemestane by a self-report questionnaire. After one year, vaginal dryness, decreased libido, bone/muscle aches, and sleeping difficulty were reported more significantly frequently in exemestane group, while hot flashes and less vaginal discharge were reported more significantly in tamoxifen group. No significant differences in vaginal bleeding, mood change, impaired word finding or low energy were observed.

Schilder CM and colleagues examined the cognitive functioning related to either tamoxifen or exemestane, and compared it with that of non-cancer subjects.[155, 156] The

first cognitive testing examined patients following doxorubicin/cyclophosphamide (AC) chemotherapy. It revealed no statistically significant differences between tamoxifen or exemestane users. Results from this test also suggested that tamoxifen use is possibly associated with worse verbal functioning, while exemestane use is possibly associated with slower manual motor speed. Both groups performed significantly worse on verbal fluency and information processing speed than healthy controls.[151] The second cognitive testing examined patients following tamoxifen. It revealed that tamoxifen use was related to statistically significant lower verbal memory functioning and executive functioning, whereas exemestane use was not related to statistically significant lower cognitive functioning.[152]

Thomas et al.[157] investigated the improvement of hot flashes, mood and QoL of postmenopausal women switching to an AI after tamoxifen. The FACT-B + ES, Hot Flashes Diary (HFD), Mood Rating Scale (MRS), Arthralgia Grading System and Patient Preference Questionnaire were used. All women had significant hot flashes at trial entry. The hot flashes score, total mean combined FACT+ES score, endocrine subscale score, and Mood Rating Scale (MRS) score significantly improved. The overall arthralgia rate at three months was higher in patients receiving AI (AI 47% vs. tamoxifen 30%; $p = 0.0001$). At six weeks, 72% patients preferred to remain on an AI, while at or after three months, 58% preferred to remain on an AI.

Mamounas EP et al.[158] conducted a QoL sub-study to compare self-reported symptoms on patients treated with exemestane with those treated with placebo. MENQOL was assessed through 24 months of follow-up. In this sub-study, compliance with questionnaires was from 80% to 97%. No significant treatment effects were noted in the vasomotor, psychosocial, physical, or sexual scales, even though patients receiving exemestane had higher symptom severity in numerical form on all of these four scales.

Boehm et al.[159] evaluated the side effects caused by tamoxifen treatment and its influence on the quality of life. A 50-item self-administrated questionnaire was designed and used on the bases of the Functional Living Index Cancer (FLIC) and FACT-B. This survey reported that breast cancer patients experienced significant impaired QoL. Tamoxifen treatment was negatively associated with the physical,

emotional and social functioning, and most of psychosocial issues (e.g., loss of vitality, loss of energy, loss of femininity, mood swings, irritability, nervous feeling or difficulties in concentrating). But loss of sexual interest showed no significant correlation with overall.

Crew KD et al.[160] investigated AI-related joint symptoms in postmenopausal women taking AIs for early-stage breast cancer. A 25-item self-administered questionnaire was performed to assess the presence of joint symptoms. 47% of the patients reported AI-related joint pain and 44% reported AI-related joint stiffness. Compared with patients who did not receive tamoxifen, patients who had tamoxifen therapy previously had lower probability to develop AI-related joint stiffness (Odds Ratio 0.40; $p < 0.05$).

Henry NL et al.[161] investigated musculoskeletal symptoms of early stage breast cancer patients treated with AI therapy with at least six months follow-up. In order to assess changes in musculoskeletal symptoms, patients completed the Health Assessment Questionnaire (HAQ) and Visual Analog Scale (VAS) at baseline, 1, 3, 6, and 12 months, respectively. The median time from initiation of AI to onset of symptoms was 1.6 months. 45.4% of the patients met criteria for rheumatologic referral. Referred patients had statistically significantly higher HAQ and VAS scores at baseline and referral. At the time of referral, the median HAQ and VAS score for referred patients were 0.375 and 51 respectively. At the time of rheumatology evaluation, the primary symptoms were joint pain and stiff joints. Other reported symptoms included muscle pain, morning stiffness, tingling, numbness, and joint swelling. After median 6.1 months, 13 patients discontinued AI therapy due to musculoskeletal toxicity.

Ruhstaller T et al.[134] used a validated self-reporting measurement - the Checklist for Patients with Endocrine Therapy (C-PET) to assess the overall frequency of subjectively experienced symptoms by patients receiving endocrine therapy. Then they compared these symptoms with side effects reported in pivotal trials – the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trial, and the Breast International Group (BIG) 1-98 Study. Only the reporting of weight gain and hot flashes/sweats was significantly greater for those receiving adjuvant therapies compared to those with metastatic disease. The following symptoms were significantly more often recorded by

the women in the adjuvant setting completing the C-PET than by physicians' reports in pivotal trials: hot flashes/sweats, low energy, fluid retention and vaginal dryness. Similar differences were observed in the metastatic and adjuvant setting.

Ochayon L et al.[162] described symptoms and QoL of breast cancer patients receiving adjuvant hormonal therapy through the FACT-B + ES and a socio-demographic and medical information questionnaire. It was found that fewer symptoms were correlated with higher QoL, but the mean QoL score for the participants was higher than that for a healthy population. Among all the symptoms, mood swings and irritability were strongly associated with a decrease in QoL. In addition, patients who exercised had higher QoL scores.

Mouridsen H et al.[163] compared letrozole and tamoxifen in the first-line therapy of advanced breast cancer postmenopausal women according to Karnofsky Performance Status (KPS). For both treatment groups, the distributions of baseline KPS scores were similar. Compared with tamoxifen group, time to worsening of ≥ 20 points in KPS score was significantly longer in letrozole group (Hazard Ratio 0.62; p = 0.001), but KPS was relatively insensitive to change in these patients. In patients with mainly lung metastases, significantly fewer letrozole patients than tamoxifen patients experienced deteriorations in their KPS scores by at least 20 points (letrozole 14% vs. tamoxifen 30%; p=0.0003), and letrozole had higher odds of improvement in KPS score by at least 20 points (Hazard Ratio 2.67; p = 0.0631). These data demonstrated that letrozole was superior over tamoxifen.

Summary

As the survival rate of breast cancer patients is increasing, issues concerning patient tolerability and QoL become increasingly important. The side effect profiles of hormonal therapies can affect patient-rated HRQoL outcomes. However, there is a dearth of the QoL information from randomized trials of hormonal therapy.

In this breast cancer hormonal therapy QoL review, two questionnaires were widely used: the Functional Assessment of Cancer Therapy-Breast (FACT-B) plus Endocrine Subscale (ES), and the Menopause Specific Quality of Life (MENQOL).

Both of them contain the specific items for assessing the hormonal therapy related side effects.

The FACT-G is the first questionnaire of the Functional Assessment of Chronic Illness Therapy (FACIT) continuum to assess cancer therapy.[164] It measures general aspects of QoL among cancer patients. It consists of 27 items for the assessment of four domains of QoL: Physical Well-Being (PWB) (seven items), Socio-Family Well-Being (SFWB) (seven items), Emotional Well-Being (EWB) (six items), and Functional Well-Being (FWB) (seven items). Patients are asked to score each item for the past week on a 4-point scale (0 = "not at all", 1 = "a little bit", 2 = "somewhat", 3 = "quite a bit", 4 = "very much"). The scores of PWB, SFWB, and FWB range from 0 to 28 points. The scores of EWB range from 0 to 24 points. The total FACT-G score is the sum of the above four subscale scores and ranges from 0 to 108. The FACT-G has been demonstrated to be valid and reliable.[164] The FACT-B measures general QoL associated with cancer (27 questions referred to the FACT-G), as well as additional dimensions more specific to breast cancer patients (nine questions).[165] The Endocrine Subscale (ES) comprises 18 items. It is designed to use with the FACT-B. Four other items related to endocrine (sleep, fatigue, nervousness and nausea) are included in the FACT-G already.[166] The FACT-B plus ES is proved to be reliable and validated.[165, 166]

The Menopause Specific Quality of Life (MENQOL) is a validated QoL tool that measures the level of discomfort associated with menopause related symptoms.[167] It consists of 29 items covering vasomotor, physical, psychosocial and sexual domain. The score for each item is from 1 to 8, with lower scores presenting lower levels of discomfort or better quality of life.

In the above studies, patients receiving hormonal therapies experienced a decreased QoL. Although QoL studies generally indicated that AIs were tolerated well and had no greater impact on QoL than tamoxifen, these hormonal therapies affected slightly different domains. Compared with patients taking tamoxifen, fewer cases of thromboembolic and gynecological events (vaginal discharge and bleeding), as well as a lower incidence of endometrial cancer were observed in those taking AIs. Side effects that were more frequent with adjuvant AI therapy in comparison to tamoxifen included

arthralgia and myalgia, joint discomfort, bone loss, decreased libido, vaginal dryness and dyspareunia, and cardiovascular system and blood lipids problems. However, the side effects could not be attributed to hormonal therapies alone. Many symptoms experienced by women in these studies were age or menopause related. In addition, some studies included patients that had received chemotherapy before, which could also produce unexpected side effects.

In summary, despite that different trial design and instruments were used to assess QoL, the results of the QoL studies included in the above review were very similar. They showed that although the side effect profiles of tamoxifen and AIs varied significantly, there were no clinically important differences in overall QoL.

3.3.2 Studies on Patient Satisfaction with Medication

Treatment satisfaction is a growing research area in particular in chronic illnesses field. It is recognized as an important outcome measure in many chronic diseases (e.g., coronary heart disease, arthritis, migraine, diabetes, asthma and rheumatoid arthritis).[133] However, this endpoint has barely been considered with regard to cancer treatment. There is a paucity of research assessing cancer medication satisfaction. This section will firstly present the studies on patient satisfaction with breast cancer-related medications. Then the studies on factors affecting patient satisfaction with medication will be documented.

Patient Satisfaction with Breast Cancer-related Medications

The studies focusing on satisfaction with breast cancer-related medication are limited. Only three studies were identified.

Carlsson et al.[168] examined the differences of the quality of life/ life satisfaction between Swedish women with breast cancer treated with complementary/anthroposophical care and matched patients treated with conventional treatment. The quality of life was measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC

QLQ-C30) and the Life Satisfaction Questionnaire (LSQ). LSQ consists of 34 items covering six different dimensions: physical symptoms, sickness impact, quality of everyday activities, socioeconomic situation, quality of family relation and quality of close friend relationship. These items are answered and scored from 1 (very much) to 7 (not at all), with higher score indicating greater life satisfaction. Then the scores of these items are summarized and transformed to range from 0 to 100, where 100 indicates maximum quality of life on each subscale.[168] This study revealed that the women who had chosen anthroposophical care increased their perceived quality of life or life satisfaction. There were significant improvements in emotional functioning and in overall quality of life in the EORTC QLQ-C30. In the LSQ improvement was seen in physical symptoms, sickness impact, quality of everyday activities and socioeconomic situation. There were no significant changes in any of the scales/factors in women who had chosen conventional medical treatment.

A study examined the impact of potential determinants for early-stage breast cancer patients' preferences for adjuvant chemotherapy by the treatment preference instrument.[169] Patients in the chemotherapy group were matched with patients in the no-chemotherapy group. In the chemotherapy group, patients were scheduled for adjuvant chemotherapy before (T1), during (T2), and 1 month after chemotherapy (T3). Then the elicited preferences were compared to responses from patients in the no-chemotherapy group. At all measurement points, the patients in the no-chemotherapy group needed more benefit from adjuvant chemotherapy before they would be willing to accept this treatment than those in the chemotherapy group. The differences were significant ($p < 0.01$). Of the demographic variables, a statistically significant relationship between age and preferences was found only at T2 in the no-chemotherapy group. This study also point out that compared with the positive experience of the treatment, reconciliation with the treatment decision was a more important determinant of patients' preferences.

Another study explored the possible relationship between patient satisfaction with antiemetic treatment and quality of life (QoL).[170] Antiemetic drugs are one of the most common used drugs for relieving the side effects produced by chemotherapy in cancer treatment. The study sample consisted of 136 chemotherapy patients with breast cancer. QoL was evaluated using the Rotterdam Symptom Checklist (RSCL).

At day five after chemotherapy, 55 of the 136 patients were very satisfied, 65 were satisfied, and 16 were unsatisfied with antiemetic treatment. Patient statement of satisfaction was related to psychological distress ($p = 0.002$), physical symptom distress ($p = 0.002$), activity level ($p = 0.002$), the control of nausea ($p < 0.01$) and vomiting ($p < 0.0001$).

Factors affecting Patient Satisfaction with Medication

Patient satisfaction with medication is not only affected by the treatment, but also by patient characteristics and social factors, such as patients' age, medication and health characteristics, and physician or pharmacists' advice. With the absence of breast cancer studies on this topic, the studies chosen below could still demonstrate the same principles.

Cohen G[171] made an attempt to relate satisfaction to age and self-reported health status in Scotland. The items on patient satisfaction were taken from a general population health survey. It was reported that dissatisfaction decreased markedly with age, and also showed a moderately significant association with psychosocial health status and pain.

Geitona et al.[172] conducted a cross-sectional national survey to examine medication use and satisfaction of Greek households. Satisfaction questionnaire consisted of two parts: a set of items drawn from the WHO health survey, and a set of items based on eight aspects of medication use: physician's consultation, physician's response to adverse events, pharmacists' consultation and advice, the resolution of symptoms, route of drug administration, drug tolerability, drug cost, and perceived contribution of the treatment to the improvement of health. A five-point scale (responses of "fully satisfied", "satisfied", "moderately satisfied", "poorly satisfied" and "not at all satisfied") was used to measure the rating of satisfaction. In general, except the costs, respondents reported a high level of satisfaction with every aspect of medication use examined. High degree of satisfaction with medication use was associated with elderly people, self-reported health status, city area of residence and the health insurance scheme with greater funds.

A study was conducted to examine the impact of mood on patients' quality of life and satisfaction with health service care.[173] Thirty-seven patients from a mood disorders clinic were asked to rate their current mood, quality of life, and satisfaction with health service care. The Psychiatric Affective Balance Rating Uniscale (PABRU) was designed specifically to assess the mood state of a person with affective disorders. The Spitzer Uniscale and the subscales of the Quality of Life Inventory (QOLI) were used to assess quality of life. The Patient/Staff Service Appraisal Questionnaire (P/S-SAQ) asked patients to record their satisfaction with their care. In this study, patients' rating of their current mood was highly correlated with their global quality of life rating, as well as QOLI ratings in specific domains. Only one service delivery satisfaction score was significantly associated with current mood ratings, namely the individualized care.

A cross-sectional survey was carried out to examine patients' experiences of treatment with antipsychotic medications and satisfaction with it.[174] This study used a self-administered questionnaire. Satisfaction was rated on a five-point scale (very satisfied, satisfied, not sure, dissatisfied, and very dissatisfied). 68% patients reported that they were satisfied or very satisfied with their medication and 71% stated that they found the medication helpful. These patients also pointed out that they were satisfied with the communication between them and their mental health professionals. In addition, being of non-white ethnic origin, experiencing side effects, dissatisfaction with communication with clinicians and lack of involvement in treatment decision were found to be associated with dissatisfaction with treatment (all $p < 0.05$).

Chen K et al.[175] assessed factors associated with patient satisfaction with antihypertensive therapy. The measure for medication satisfaction included the following items: overall satisfaction with the current medication, probability of continuing treatment, and probability of recommending the treatment to the other people with the similar condition. The outcomes were compared between patients who had self-reported controlled blood pressure and patients with uncontrolled blood pressure. This study reported that patients with controlled blood control had significantly better overall satisfaction with their medication ($p < 0.001$) and higher probability to continue the medication ($p < 0.001$). In addition, patients without

experiencing adverse events had significantly better overall satisfaction with their medication than patients experienced adverse events ($p < 0.001$).

Hoffman et al.[176] investigated the correlations of demographic, socioeconomic, and clinical characteristics with localized prostate carcinoma treatment satisfaction. A 24-month survey consisting of general and disease-specific measures of HRQoL, report of urinary, bowel and sexual function, the perception of any problems with these functions, and some other items regarding subsequent cancer treatments and treatment satisfaction was used. It was noted that 59.2% of patients undergoing treatment were satisfied with their treatment decisions, of which 76.8% stated that they definitely would make the same treatment decision again. Some factors, such as receiving an active treatment (50.5%), perception of being cancer free (66.4%), having urinary (64.2%) and bowel (60.5%) control, having normal erectile function (65.9%), having a good overall health (71.3%) and social support (68.1%), were significantly and positively associated with satisfaction (all $p < 0.05$). Additionally, compared with non-Hispanic men, after undergoing radical prostatectomy or androgen deprivation, Hispanic men were less satisfied.

Sanda et al.[177] examined the factors associated with quality of life in prostate cancer patients and the effects on satisfaction with the overall outcome of treatment. The Expanded Prostate Cancer Index Composite (EPIC-26) and Service Satisfaction Scale for Cancer Care (SCA) were used. This study showed that changes in quality of life (sexual function, vitality, and urinary function) were significantly correlated with the degree of outcome satisfaction among patients and their families. In comparison to patients of other racial backgrounds, blacks were significantly less satisfied with their overall treatment outcome ($p = 0.04$).

Data from the 2005 National Health and Wellness Survey were collected to evaluate the effects of individual and condition characteristics on satisfaction with overactive bladder (OAB) medications.[178] In this survey, there are questions about medication satisfaction, which was rated on a five-point scale from 1 (not at all satisfied) to 5 (extremely satisfied). In this study, satisfaction with treatment was higher among those for whom OAB interfered as little as possible with their normal daily activities.

Those who were satisfied also tended to have more frequent medication use and longer duration of use.

Bultman and Svarstad[179] used an interview questionnaire to examine the association between patient satisfaction with antidepressant medication therapy and pharmacist monitoring. It revealed that pharmacist monitoring was predictive of satisfaction and adherence for individuals taking an antidepressant for the first time. 32% patients found pharmacists helpful in solving problems related to the antidepressant.

There are some studies examining the contributing factors of satisfaction with diabetic medications. These studies reported that patients with lower education levels and lower income are less satisfied with treatment.[180] Patients having any side effects were associated with lower satisfaction with treatment.[181, 182] Additionally, satisfaction was positively associated with concurrent medications.[182] Lower self-rated mental and physical health status were correlated with lower treatment satisfaction.[181, 183]

Summary

Breast cancer is the most frequently diagnosed type of cancer among women, and most of them are treated by hormonal medications which are accompanied with different profiles of side effects. However, the QoL studies included in the above reviews showed that although the side effect profiles of tamoxifen and AIs varied significantly, there were no clinically important differences in overall QoL. Consequently, patient satisfaction, including different aspects of the treatment experience, will be particularly helpful to compare different hormonal medication treatments. Unfortunately, to date there is no study assessing patient satisfaction with breast cancer hormonal medications, especially its contributing factors. Therefore, it is important to know how tamoxifen and AIs impact breast cancer patients' satisfaction, and serve as the baseline for the policy makers on how to possibly improve breast cancer outcomes over time. A number of predictors for satisfaction with medications have been identified from previous studies, such as side effects, concurrent medication use, long-term and consistent use of medication, and self-reported health status.

3.4 Methodology

This study compares the side effects reported by breast cancer patients with different hormonal medications, and then examines both individual and condition characteristics that affect patient satisfaction with these medications. Nowadays, various media are available for collecting patient-reported outcomes (PROs), and the Internet is increasingly recognized as an important source of information. In addition to the wide availability and easy access to the Internet, patients' turning to the Web is mainly due to the dissatisfaction with the information provided by health care providers. When patients experience significant side effects, their needs for therapy modifications and supportive care often change.[184] Although patients consider their health care providers to be the most trusted source of health information, they are often dissatisfied with the information provided to them. Two studies reported that 87% of cancer patients stated that they wanted as much information about their illness as possible,[185,186] of which approximately 54% feel that their health care providers did not provide them with adequate information.[186] Studies focusing on breast cancer patients revealed that many patients desired to get more detailed information, especially they want to collaborate with their physician in major treatment decision.[187] Providing information as much as possible to cancer patients could help these patients reduce anxiety, improve drug compliance, gain better control, promote participation and self-care, generate feelings of safety, and create sensible expectations.[188]

There is a noteworthy finding that the quality of cancer information from the Internet is not so bad after all in comparison to other topic areas. A study examined patient and caregiver's interest in Internet-based cancer services. It indicated that 80% cancer patients and their caregivers were interested in treatment-related information on the Internet, and 65% expressed an interest in online support groups.[189] Currently, breast cancer is one of the most common health related search topics from the Internet,[190] and the quality of information about it on the web is more complete and accurate than about other topic areas.[190, 191] Studies assessing the accuracy of cancer websites have found that the inaccuracy rate is 5.1% for breast cancer,[191] 9% for English or 4% for Spanish breast cancer documents.[192]

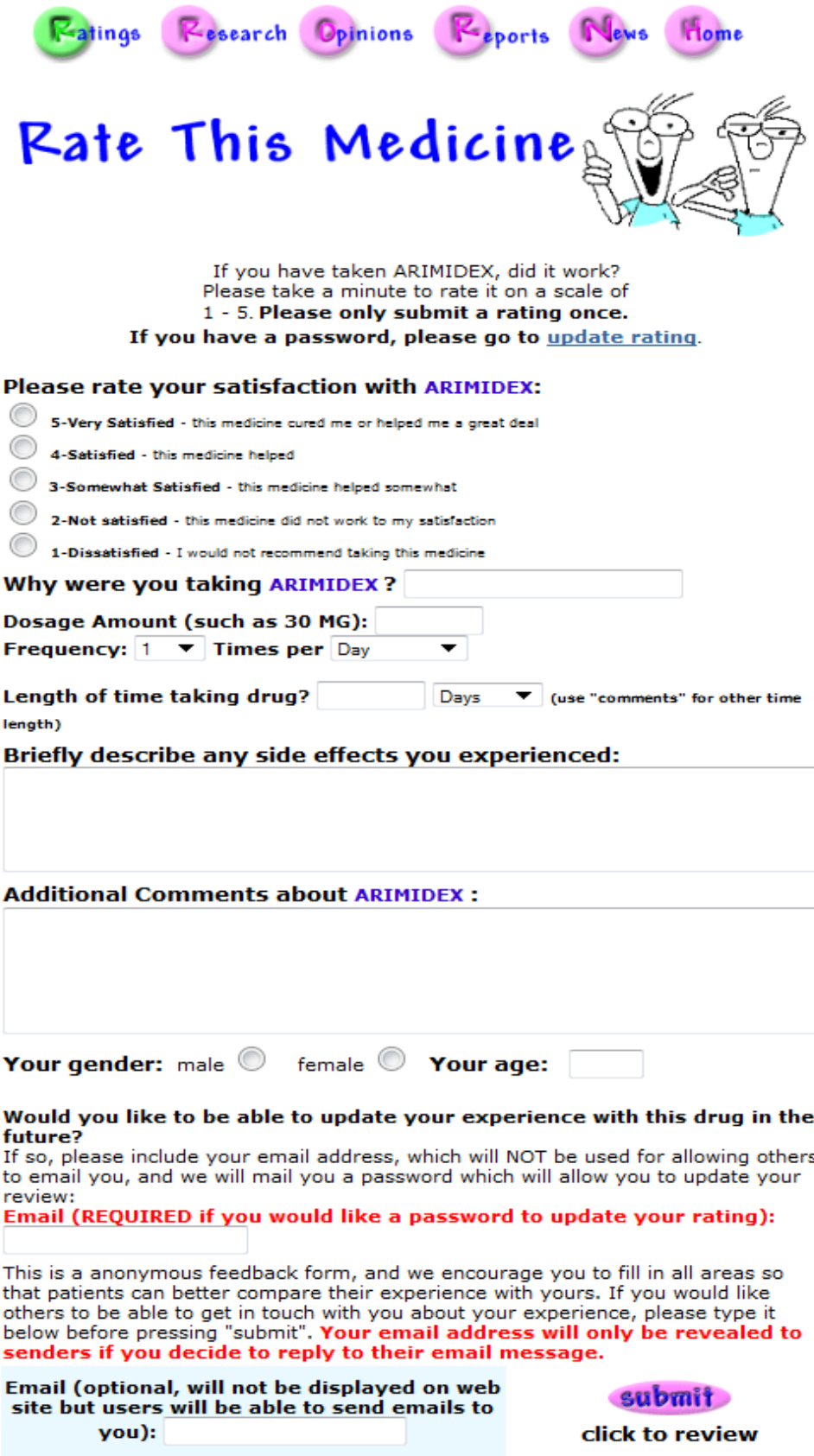
This section will firstly introduce the data source. Secondly, the study sample and variables will be presented. Thirdly, it will describe the statistical analytic methods used in this study.

3.4.1 Data Source

The patient self-reported data in this study was collected from an Internet website www.askapatient.com. This website is designed to provide information about patients' experience with prescribed drugs approved by the FDA, such as brand names, prescription purpose, usage instruction, special precautions, side effects, and more. On the website, patients can rate their medications and share comments with other patients about a range of medicines that they are taking or have taken.

Figure 6 uses Arimidex which is the brand name of anastrozole as an example to illustrate how breast cancer patients rate this hormonal medication. Firstly, patients are asked to rate this drug on a scale from 1 (most dissatisfied) to 5 (most satisfied). Then they are asked to fill in the reason for taking Arimidex. Some basic demographic information in separate fields, including age, gender, dose and the length of time they have been taking the drug, are also needed. There are two fields available for patients to enter discursive comments: one is "Side effects" and the other one is "Comments". In both fields, respondents typically write between 25 and 100 words. Although patients are not asked to name other drugs they might be taking concurrently or previously, some patients provide such details in "Comments".

Figure 6: Website Interface



Overall, this database includes patients' demographics, drug and feedback information, which, more specifically, is the following key data elements:

- Eligibility information
  - Gender
  - Age
  - Reasons for taking drug
- Prescription drug claims
  - Days of drug supplied
  - Dosage amount
- Feedback information
  - Drug rating, the level of satisfaction is from 1 (dissatisfied) to 5 (very satisfied)
  - Self-reported side effects
  - Patient's comments, including patient usage history, experience and side effects

Reasons for Using Data from Askapatient Website

The first reason to use data from Askapatient website is that this website is so far the best resource for patient opinion about drug performance, which was established ten years ago and all the prescription drugs are currently approved by the FDA. It is a database collecting patient experience of medicine and ratings of medicine effectiveness, and also including respondents' opinion polls on healthcare topics and a section of health care research assistance.[138] Therefore, it could be said that Askapatient website is a high quality site.

Secondly, patients are asked to rate the drugs they are taking on this website. The drug-ratings reflect the information of patient satisfaction, which has been shown to associate with quality of life, and patients are more probably to feel happy with their participation in the whole process of decision making if they feel satisfied with the adequacy of information provided.[188] Additionally, satisfaction information may be served as a benchmark for health professionals to identify potential areas for service

improvement and optimize health expenditure through patient-guided planning and evaluation.[35]

The third reason is that Askapatient website enables to assess side effects without being influenced by caregivers, as it is completed by the patient without the help of nurses or consulting the doctor. Unlike the validated HRQoL questionnaire, on this website patients could list any side effect they experienced, from serious, life-threatening to minor, easy-to-manage ones.

The last reason is that all the data on Askapatient website is publicly available. These communications are analogous to public records, because the data are anonymous, and posting a comment on a drug does not require registration. Due to the anonymous nature and privacy policy of this website, conducting a passive analysis of the comments without seeking informed consent from their authors is ethically acceptable.[193] Furthermore, in terms of format, this online medium is more flexible than a face-to-face or telephone survey. Patients from different care settings and countries could share their experiences with drugs.

3.4.2 Definitions of Study Sample and Variables

This section will present the study sample and a short explanation about the patient and condition characteristics which could influence satisfaction.

3.4.2.1 Study Sample

The analysis of this study was confined to drugs that had at least 30 patient entries, as of April 28th, 2010. Patients' self-reported socio-demographic, drug and feedback data were collected. Due to the missing information about the dosage amount before February, 2010, this kind of information is not taken into account. To be eligible for inclusion, patients were required to

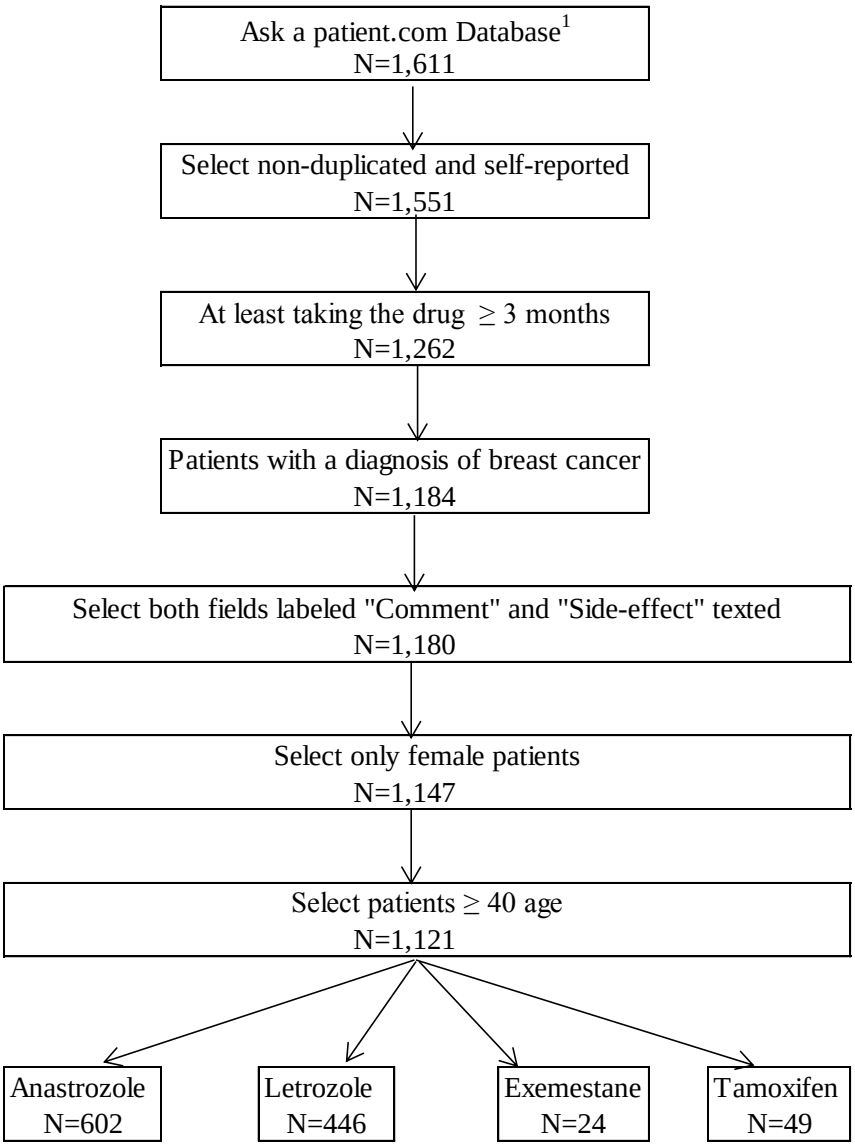
- have an diagnosis for breast cancer,

- be female patients, because the percentage of male breast cancer patients in this database is less than 2%, which was too small for valid comparisons,
- be at least 40 years old, because 98% breast cancer patients were aged 40 and older in this database, and menopause normally happens after 40 years old,[194]
- have at least one pharmacy dispensing for any of the following drugs:
    - Anastrozole (Arimidex®)
    - Letrozole (Femara®)
    - Exemestane (Aromasin®)
    - Tamoxifen (Nolvadex®)
- take the drug for at least three months, because most symptoms occur soon after patients start hormonal treatment,[195]
- self-report all the information, and
- fill in both fields labeled "Comment" and "Side-effect".

All the entries were scrutinized. A provisional list of possible adverse events was used as a guide to examine the side effects from "Comment" and "Side-effect". This list was derived from the known side effect profiles of tamoxifen and AIs and from the literature. Additional effects and experiences were also identified during inspection of the comments. In addition, all the duplicated entries and entries submitted by relatives were excluded.

Figure 7 summarizes the inclusion criteria and final sample. Overall, 1,121 patients fulfilled the above criteria as of April 28th, 2010. All the patients were female with age greater than 40, self-reported with the diagnosis of breast cancer, and they took the hormonal medication for at least three months. For the purpose of comparing AIs with tamoxifen in breast cancer patients, four monotherapy cohorts were created from the 1,121 patients who fulfilled the above criteria: namely, tamoxifen, anastrozole, exemestane, and letrozole monotherapy cohort. These were created based on their drug dispensing and with an observation period of at least three months. Because the objective was to compare each AI to tamoxifen, the reference group was defined as the tamoxifen group, and the treatment groups were defined as each of the three monotherapy groups. In anastrozole cohort, there were 602 patients. In letrozole cohort there were 446 patients. 24 patients were in exmestane cohort and 49 patients were in tamoxifen cohort.

Figure 7: Sample Selection



Notes:

1. Counts as of 04/28/2010.

3.4.2.2 Definition of Covariates

Patient and condition characteristics that could influence satisfaction were included in the multivariate analyses. Below is a list of these covariates with a short explanation.

Age

Dummies were used to account for different age categories: 40 - 64 years, and above 65 years. Age can also be used as a continuous variable.

Treatment Duration

The duration of hormonal medication treatment was unified in months.

Concurrent Drug Use

For relieving the side effect, such as hot flashes, pain, depression, nausea, vaginal dryness etc., some other drugs were also taken at the same time. A dummy was used to identify each of these medications that had concurrent drug use or has mono-drug use. Value 1 indicated concurrent drug use, while value 0 indicated mono-drug use.

Prior Drug Use

In order to identify whether each of these medications switched from another drug or not, a dummy was used. Value 1 indicated switching from another drug, while value 0 indicated not switching.

Currently taking Medication Status

A dummy was used to identify if the patients were currently still taking medication or not. Value 1 indicated currently still taking medication, while value 0 indicated medication withdrawal.

3.4.3 Statistical Analytic Methods

Statistical analyses are performed using SAS software version 9.2 (SAS Institute, Cary, NC). All tests for statistical significance were two-sided, and the 5% level was used as cutoff for statistical significance.

Descriptive Analysis

Patient characteristics, such as demographics and medical history, were described for each cohort. Side effects experienced by patients after taking tamoxifen and AIs were also reported separately.

Descriptive statistics and correlations between these variables were computed based on the frequencies and percentages for categorical variables, mean and standard deviation for continuous variables. Categorical variables were compared using Pearson χ^2 test or Fisher's exact test to know if the characteristics of an AI cohort were significantly different from those of tamoxifen group. Continuous variables were compared using Wilcoxon rank sum test for non-parametric variables, and two-sided Student's t-test for normally distributed variables.

Multivariate Analysis

a) Comparison of Side Effects

Most symptoms occur soon after patients start hormonal treatment,[195] thus the recording of these symptoms at the initial three-month follow-up visit was used as the measure of symptom occurrence. Tamoxifen group was used as the reference group to facilitate comparisons with other therapeutic options. Unadjusted and adjusted Incidence Rates Ratio (IRR) and Odds Ratio (OR) were estimated between study cohorts.

IRR referred to the side effects incurred during the three-month study period by tamoxifen patients versus AIs patients. OR evaluated the likelihood of tamoxifen patients having at least one occurrence of side effects during the three-month study period compared to that of AIs patients.

Statistically significant differences between the cohorts were tested using generalized linear model (GLM) regression models with a log link and a Poisson distribution for IRR and logistic regression models for OR. Results were presented as

IRR and OR. 95% confidence intervals (CIs) were calculated. Multivariate regression models were controlled for age, duration of medication, concurrent drug use, and prior drug use.

b) Comparison of Satisfaction

To capture the factors affecting patient satisfaction with medications, two multivariate analyses were conducted. One is the comparison between satisfaction and non-satisfaction. The other one is the comparison of satisfaction levels.

Comparison between Satisfaction and Non-Satisfaction

The probability of being satisfied for patients treated with tamoxifen was compared with that of patients treated with AIs. A logistic regression approach was used with satisfaction as the dependent variable. Independent variables included age, duration of medication, concurrent drug use, prior drug use, currently taking hormonal medication status, and most common side effects. Here, the dependent variable satisfaction was dichotomous, and it was coded as:

- 1 (drug rating $\geq$ 3)
- 0 (drug rating $<$ 3)

Value 1 indicated satisfaction, while value 0 indicated non-satisfaction. Proc genmod with link=logit, dist=binominal options was performed in the binary logistic regression. OR evaluated the probability of AIs patients experiencing satisfaction compared to that of tamoxifen patients. The adjusted OR was reported with their respective p-values (using tamoxifen as the reference group). Differences across cohort levels were tested for statistical significance.

Comparison of Satisfaction Levels

The likelihood of rating a higher drug-rating in the group of patients treated with tamoxifen was compared with that of patients treated with AIs. An ordinal logistic

regression was used. Here, the dependent variable – drug-rating of satisfaction – was polytomous, and it was coded in descending order: 5 = Very Satisfied, 4 = Satisfied, 3 = Somewhat Satisfied, 2 = Not Satisfied, 1 = Dissatisfied. Proc logistic was used with the link=clogit option. Here, clogit stands for cumulative logit.

OR evaluated the likelihood of AIs patients rating a higher score compared with that of tamoxifen patients. The covariates used in multivariate analyses were age, duration of hormonal medication, concurrent drug use, prior drug use, currently taking hormonal medication status, and most common side effects. The adjusted OR was reported with their respective p-values (using tamoxifen as the reference group). Differences across cohort levels were tested for statistical significance.

3.5 Results

The first section describes and compares the patient characteristics. The second section provides the comparison of side effects reported by patients taking tamoxifen and AIs. Age, duration of hormonal medication, concurrent drug use, and prior drug use are controlled for multivariate analyses. The third section includes the impact of each AI and tamoxifen cohorts on the satisfaction rating separately. Then the results of multivariate analyses are presented.

3.5.1 Patient Characteristics

Table 19 describes overall patient characteristics. At the time of the study, most patients were in the 50-59 age range. Compared with AIs cohorts, more tamoxifen patients were in the 40-49 age range, while less tamoxifen patients were aged older than 60 years. In every AIs cohort, the mean age of patients was significantly older than that in tamoxifen cohort ($p < 0.05$). For the AIs cohorts, all of the mean age was more than 55 years old. For the tamoxifen cohort, the mean age was 52.7 years (SD = 8.4). With regard to the treatment duration, those taking anastrozole had been taking their drug 3 months longer than those taking tamoxifen. Compared with tamoxifen group, the duration of letrozole and exemestane treatments was shorter (19.3 months,

15.3 months, 19.7 months for letrozole, exemestane and tamoxifen respectively). However, these differences were not statistically significant.

Table 19: Characteristics of Breast Cancer Patients with Hormonal Medications

Characteristics	Tamoxifen [1] N=49	Anastrozole N=602		Letrozole N=446		Exemestane N=24	
	N (%)	N (%)	P-Value [2]	N (%)	P-Value [2]	N (%)	P-Value [2]
Age Distribution							
40-49 Years	19 (38.8%)	92 (15.3%)	0.0002 **	88 (19.7%)	0.0052 **	3 (12.5%)	0.0294
50-59 Years	19 (38.8%)	303 (50.3%)	0.1379	238 (53.4%)	0.0699	15 (62.5%)	0.0806
60+ Years	11 (22.4%)	207 (34.4%)	0.1146	120 (26.9%)	0.6097	6 (25.0%)	0.8086
Age (years; Mean ± SD)	52.7±8.4	57.0±7.4	<.0001 **	55.7±7.2	0.002 **	56.0±6.9	0.031 *
Duration of Treatment in Months (Mean ± SD)	19.7±29.1	22.6±18.6	0.0741	19.3±17.5	0.5776	15.3±7.6	0.4659
Treatment History							
Prior Drug Use	9 (18.4%)	107 (17.8%)	0.8482	146 (32.7%)	0.0504	13 (54.2%)	0.0028 **
AI	5 (10.2%)	10 (1.7%)	0.0033 **	39 (8.7%)	0.7900	8 (33.3%)	0.0230 *
Tamoxifen	-	92 (15.3%)	0.0009 **	116 (26.0%)	<.0001 **	11 (45.8%)	<.0001 **
Concurrent Drug Use	2 (4.1%)	21 (3.5%)	0.6890	8 (1.8%)	0.2595	3 (12.5%)	0.3229
Current Still Taking Medication	27 (55.1%)	250 (41.5%)	0.0720	142 (31.8%)	0.0022 **	9 (37.5%)	0.2140

Notes:

[1] Tamoxifen is the reference group.

[2] P-values are based on Fisher's exact tests for categorical variables, Wilcoxon rank sum test for continuous variables.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

SD: Standard Deviation

Approximately 24% of all patients explicitly reported that they had switched from another drug. The difference between tamoxifen and anastrozole was not evident (tamoxifen 18.4% vs. anastrozole 17.8%). In anastrozole group, about 15.3% patients took tamoxifen previously, and only 1.7% patients took other AIs previously. These differences were statistically significant ($p < 0.01$). Although more patients taking letrozole had prior drug use than patients taking tamoxifen, no significant difference was recorded ($p = 0.0504$). In letrozole group, approximately 26% patients had switched from tamoxifen ($p < 0.0001$), and 8.7% patients had switched from the other AIs. Exemestane group had the highest percentage of patients who had prior drug use (54.2%), and compared with tamoxifen, this difference was statistically significant ($p = 0.0028$). Almost half number of patients (45.8%) used tamoxifen prior to exemestane, and 33.3% patients used to take the other AIs prior to exemestane. For tamoxifen cohort, 10.2% users used AIs previously.

For relieving the side effect, such as hot flashes, pain, depression, nausea, vaginal

dryness etc., some other drugs were also taken at the same. Compared with other three cohorts, more patients had concurrent drug use with exemestane to relieve side effects, which accounted for 12.5%. Letrozole group has the lowest percentage of patients who took concurrent drug, which was 1.8%. However, significant differences were barely recorded.

Moreover, compared with patients taking AIs, more patients taking tamoxifen insisted on taking it, which was more than half percentage. There was a significantly lower rate of insisting on taking letrozole than tamoxifen (letrozole 31.8% vs. tamoxifen 55.1%, p = 0.0022).

Table 20 presents the reasons for stopping current hormonal medication. Among the patients who stopped the current medication, more than 80% explicitly reported that they withdrew because of the side effects. Besides side effects, there were some other reasons that patients chose to withdraw the medication. One out of the seven exemestane patients and two out of the 18 tamoxifen patients reported that the reason was the ineffectiveness of the medication. Some patients complained that the medication was too expensive, they could not afford it. Some patients stopped the medication due to the finish of treatment. Less than 2% patients did not explain why they stopped taking anastrozole.

Table 20: Reasons for Stopping Medication Treatment

Drug Class	Stop due to side effects	Stop due to the ineffectiveness of the drug	Stop due to other reasons	Not reported
	N (%)	N (%)	N (%)	N (%)
Aromatase Inhibitors				
Anastrozole (Arimidex®)	105 (93.8%)	-	5 (4.5%)	2 (1.8%)
Letrozole (Femara®)	71 (94.7%)	-	4 (5.3%)	-
Exemestane (Aromasin®)	6 (85.7%)	1 (14.3%)	-	-
SERM[1]				
Tamoxifen (Nolvadex®)	15 (83.3%)	2 (11.1%)	1 (5.6%)	-

Notes:

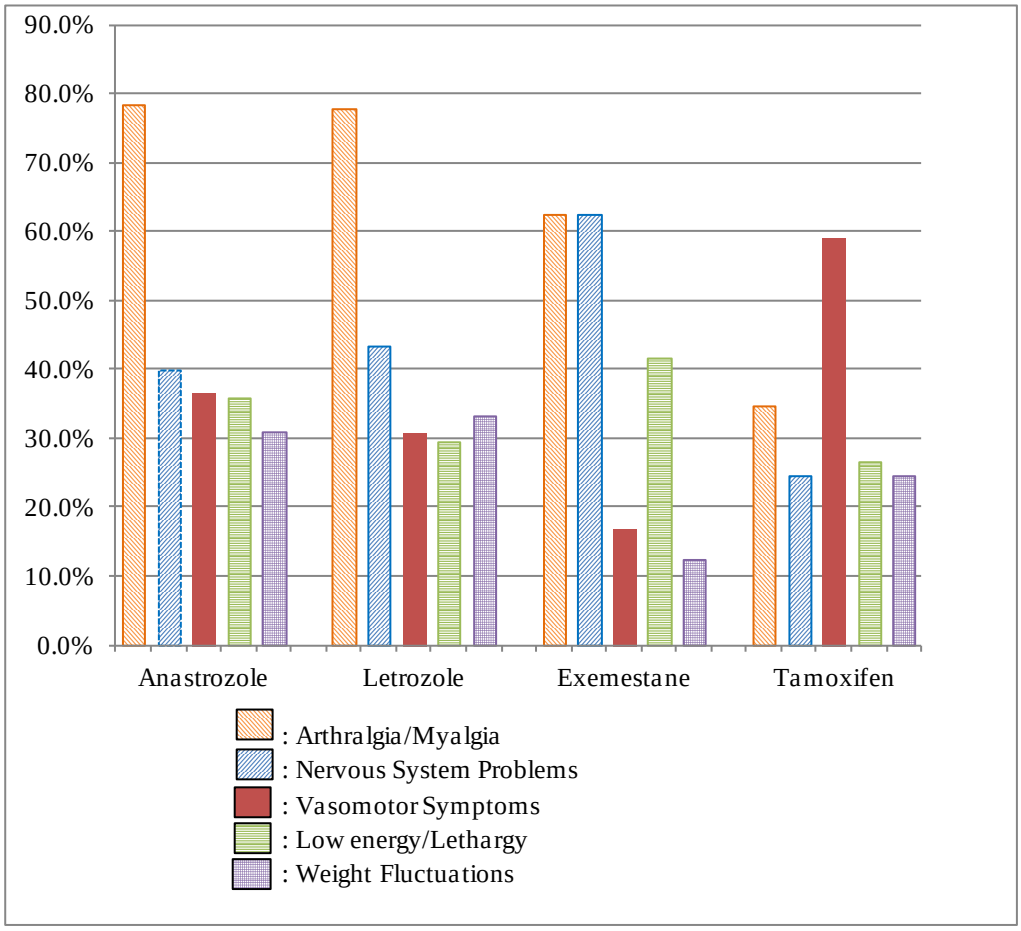
1. Selective Estrogen Receptor Modulators

3.5.2 Comparison of Side Effects

Different hormonal medications are associated with different side effects profiles which may be specific to individual patient. In this study, musculoskeletal disorders included pain (arthralgia, myalgia, bone pain), stiff joint, swollen joint, trigger fingers, muscle weakness, and cramps. Hot flashes and sweats were considered vasomotor symptoms. Gynecologic side effects consisted of loss of libido, vaginal dryness, dyspareunia, vaginal discharge/bleeding, and other serious side effects, such as ovarian cysts and uterine fibroid. Headache, dizziness, Carpal Tunnel Syndrome (CTS) and neuropathy were parts of nervous system problems. CTS is a condition with pain and muscle weakness or numbness in the fingers, hand and wrist, even the arm, because the median nerve is pressed or squeezed at the wrist.[196] Neuropathy is a disorder in the function of a nerve or particular group of nerves.[197] The most common form is peripheral neuropathy, which refers to the damage to the peripheral nerves that connect the spinal cord to muscles, skin and internal organs.[198] It mainly affects the feet and legs, and it is among the most common neurologic complication of cancer.[199] In this study, neuropathy was composed of hand/foot pain, stiffness, swelling, difficulty of walking and standing, and off balance. Mental awareness included loss of memory, loss of concentration, confusion, forgetfulness, and cognitive difficulty. Skin problems and alopecia were considered dermatologic side effects.

Figure 8 illustrates the top five most common side effects reported across all four cohorts. They were arthralgia or myalgia, nervous system problems, vasomotor symptoms, low energy/lethargy and weight fluctuations. It was evident that arthralgia or myalgia was most commonly recorded for AIs, while tamoxifen was associated with the most frequent complaints of vasomotor symptoms. Exemestane had more complains about nervous system problems and less complains about weight fluctuations than anastrozole, letrozole or tamoxifen.

Figure 8: Top 5 Most Common Side Effects Reporting Rates



3.5.2.1 Descriptive Analysis

Table 21 describes the proportions of patients experiencing different side effects, and presents the results of Fisher's exact test of the difference in the distributions of effects among the four cohorts. It shows that AIs patients experienced significantly more musculoskeletal symptoms, nervous system problems and sleep disorders than tamoxifen patients. In contrast, tamoxifen patients experienced significantly more vasomotor symptoms than AI patients. There were no differences of osteopenia, mental awareness, mood disorders, dermatologic side effects, weight change, low energy/lethargy, gastrointestinal symptoms and cardiovascular disease. A small number of people (< 5%) taking each sort of drug reported high cholesterol, eye problems, urinary tract problems, liver/lung/bladder problems, dry mouth, edema etc., which were too small for valid comparisons.

Table 21: Frequencies of Side Effects Reported by Breast Cancer Patients with Hormonal Medications

Side Effects	Tamoxifen [1] N=49	Anastrozole N=602		Letrozole N=446		Exemestane N=24	
	N (%)	N (%)	P - Value[2]	N (%)	P - Value[2]	N (%)	P - Value[2]
Musculoskeletal Symptoms	21 (42.9%)	515 (85.5%)	<.0001 **	378 (84.8%)	<.0001 **	17 (70.8%)	0.0282 *
Pain	17 (34.7%)	493 (81.9%)	<.0001 **	362 (81.2%)	<.0001 **	16 (66.7%)	0.0130 *
Arthralgia/Myalgia	17 (34.7%)	473 (78.6%)	<.0001 **	348 (78.0%)	<.0001 **	15 (62.5%)	0.0434 *
Bone pain	3 (6.1%)	75 (12.5%)	0.2533	57 (12.8%)	0.2477	3 (12.5%)	0.3876
Joint-Stiffness	1 (2.0%)	80 (13.3%)	0.0215 *	43 (9.6%)	0.1076	2 (8.3%)	0.2500
Joint-Swelling	0 (0.0%)	21 (3.5%)	0.3932	22 (4.9%)	0.1514	0 (0.0%)	-
Trigger Fingers	0 (0.0%)	47 (7.8%)	0.0405 *	28 (6.3%)	0.0971	3 (12.5%)	0.0325 *
Muscle Weakness	1 (2.0%)	9 (1.5%)	0.5453	9 (2.0%)	1.0000	0 (0.0%)	1.0000
Cramps	7 (14.3%)	12 (2.0%)	0.0002 **	10 (2.2%)	0.0006 **	0 (0.0%)	0.0877
Osteopenia	0 (0.0%)	43 (7.1%)	0.0655	25 (5.6%)	0.1583	1 (4.2%)	0.3288
Nervous System Problems	12 (24.5%)	241 (40.0%)	0.0332 *	194 (43.5%)	0.0139 *	15 (62.5%)	0.0022 **
Headache	2 (4.1%)	42 (7.0%)	0.7646	33 (7.4%)	0.5609	2 (8.3%)	0.5937
Dizziness	3 (6.1%)	16 (2.7%)	0.1657	17 (3.8%)	0.4356	0 (0.0%)	0.5462
Carpal Tunnel Syndrome	1 (2.0%)	63 (10.5%)	0.0756	43 (9.6%)	0.1076	8 (33.3%)	0.0004 **
Neuropathy	10 (20.4%)	177 (29.4%)	0.2496	149 (33.4%)	0.0760	13 (54.2%)	0.0065 **
Gynecologic Side Effects	10 (20.4%)	145 (24.1%)	0.7272	134 (30.0%)	0.1864	2 (8.3%)	0.3146
Loss of Libido	0 (0.0%)	100 (16.6%)	0.0003 **	76 (17.0%)	0.0003 **	2 (8.3%)	0.1050
Vaginal Dryness	4 (8.2%)	67 (11.1%)	0.6398	81 (18.2%)	0.1079	0 (0.0%)	0.2955
Dyspareunia	0 (0.0%)	8 (1.3%)	1.0000	9 (2.0%)	0.6091	0 (0.0%)	-
Vaginal Discharge/Bleeding	5 (10.2%)	9 (1.5%)	0.0024 **	3 (0.7%)	0.0003 **	0 (0.0%)	0.1644
Other [3]	4 (8.2%)	3 (0.5%)	0.0008 **	2 (0.4%)	0.0011 **	0 (0.0%)	0.2955
Vasomotor Symptoms	29 (59.2%)	220 (36.5%)	0.0022 **	137 (30.7%)	0.0001 **	4 (16.7%)	0.0009 **
Hot Flashes	26 (53.1%)	206 (34.2%)	0.0123 *	118 (26.5%)	0.0002 **	3 (12.5%)	0.0009 **
Sweats	7 (14.3%)	42 (7.0%)	0.0836	42 (9.4%)	0.3095	2 (8.3%)	0.7085
Mental Awareness	10 (20.4%)	118 (19.6%)	0.8530	91 (20.4%)	1.0000	7 (29.2%)	0.5563
Loss of Memory	5 (10.2%)	81 (13.5%)	0.6626	59 (13.2%)	0.6588	6 (25.0%)	0.1606
Loss of Concentration	4 (8.2%)	50 (8.3%)	1.0000	32 (7.2%)	0.7715	2 (8.3%)	1.0000
Confusion	4 (8.2%)	35 (5.8%)	0.5249	26 (5.8%)	0.5238	2 (8.3%)	1.0000
Forgetfullness	3 (6.1%)	32 (5.3%)	0.7409	35 (7.8%)	1.0000	2 (8.3%)	1.0000
Cogitive Difficulty	2 (4.1%)	3 (0.5%)	0.0480 *	5 (1.1%)	0.1462	0 (0.0%)	1.0000
Sleep Disorders	2 (4.1%)	123 (20.4%)	0.0038 **	97 (21.7%)	0.0021 **	7 (29.2%)	0.0046 **
Mood Disorders	7 (14.3%)	148 (24.6%)	0.1178	105 (23.5%)	0.1546	4 (16.7%)	1.0000
Anxiety	0 (0.0%)	23 (3.8%)	0.4063	19 (4.3%)	0.2405	1 (4.2%)	0.3288
Mood Swing	2 (4.1%)	61 (10.1%)	0.2135	32 (7.2%)	0.5611	0 (0.0%)	1.0000
Depression	5 (10.2%)	101 (16.8%)	0.3138	73 (16.4%)	0.3081	3 (12.5%)	1.0000

Notes:

[1] Tamoxifen is the reference group.

[2] P-values are calculated using Fisher's exact tests.

[3] Other included serious gynecologic side effects, such as ovarian cysts, uterine fibroid etc.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Table 21 (continued):

Side Effects	Tamoxifen [1] N=49	Anastrozole N=602		Letrozole N=446		Exemestane N=24	
	N (%)	N (%)	P - Value[2]	N (%)	P - Value[2]	N (%)	P - Value[2]
Dermatologic Side Effects	6 (12.2%)	133 (22.1%)	0.1452	107 (24.0%)	0.0727	2 (8.3%)	1.0000
Skin	3 (6.1%)	56 (9.3%)	0.6087	37 (8.3%)	0.7853	2 (8.3%)	1.0000
Alopecia	3 (6.1%)	87 (14.5%)	0.1312	84 (18.8%)	0.0280 *	0 (0.0%)	0.5462
Growth of Facial Hair	0 (0.0%)	8 (1.3%)	1.0000	0 (0.0%)	-	0 (0.0%)	-
Weight/Appetite Fluctuations	12 (24.5%)	187 (31.1%)	0.4205	149 (33.4%)	0.2608	3 (12.5%)	0.3568
Increase of Weight	12 (24.5%)	181 (30.1%)	0.5156	147 (33.0%)	0.2616	2 (8.3%)	0.1236
Loss of Weight	0 (0.0%)	1 (0.2%)	1.0000	2 (0.4%)	1.0000	0 (0.0%)	-
Increase of Appetite	0 (0.0%)	1 (0.2%)	1.0000	0 (0.0%)	-	0 (0.0%)	-
Loss of Appetite	1 (2.0%)	6 (1.0%)	0.4233	2 (0.4%)	0.2690	1 (4.2%)	1.0000
Low Energy/Lethargy	13 (26.5%)	217 (36.0%)	0.2145	132 (29.6%)	0.7423	10 (41.7%)	0.2832
Fatigue	9 (18.4%)	176 (29.2%)	0.1372	106 (23.8%)	0.4779	7 (29.2%)	0.3693
Weakness	1 (2.0%)	11 (1.8%)	0.6122	5 (1.1%)	0.4668	1 (4.2%)	1.0000
Loss of Energy	4 (8.2%)	50 (8.3%)	1.0000	30 (6.7%)	0.7637	3 (12.5%)	0.6770
Gastrointestinal Symptoms	3 (6.1%)	48 (8.0%)	1.0000	40 (9.0%)	0.7880	3 (12.5%)	0.3876
Nausea	1 (2.0%)	22 (3.7%)	1.0000	17 (3.8%)	1.0000	1 (4.2%)	1.0000
Constipation	1 (2.0%)	11 (1.8%)	0.6122	11 (2.5%)	1.0000	1 (4.2%)	1.0000
Diarrhea	0 (0.0%)	7 (1.2%)	1.0000	3 (0.7%)	1.0000	0 (0.0%)	-
Other [4]	2 (4.1%)	13 (2.2%)	0.3135	13 (2.9%)	0.6521	1 (4.2%)	1.0000
Cardiovascular Diseases [5]	2 (4.1%)	37 (6.1%)	0.7596	27 (6.1%)	0.7568	1 (4.2%)	1.0000
High Cholesterol	0 (0.0%)	24 (4.0%)	0.2458	25 (5.6%)	0.1583	1 (4.2%)	0.3288
Dyspnea	4 (8.2%)	6 (1.0%)	0.0043 **	5 (1.1%)	0.0074 **	1 (4.2%)	1.0000
Eye Problems [6]	2 (4.1%)	16 (2.7%)	0.6385	32 (7.2%)	0.5611	0 (0.0%)	1.0000
Urinary Tract Problems	2 (4.1%)	8 (1.3%)	0.1697	12 (2.7%)	0.6393	1 (4.2%)	1.0000
Other Side Effects	5 (10.2%)	60 (10.0%)	1.0000	14 (3.1%)	0.0309 *	0 (0.0%)	0.1644
Edema	2 (4.1%)	12 (2.0%)	0.2845	4 (0.9%)	0.1113	0 (0.0%)	1.0000
Flu-like Symptoms	0 (0.0%)	26 (4.3%)	0.2491	5 (1.1%)	1.0000	-	-
Tinnitus	0 (0.0%)	5 (0.8%)	1.0000	-	-	-	-
Dry Mouth	0 (0.0%)	10 (1.7%)	1.0000	-	-	-	-
Teeth Problems	0 (0.0%)	4 (0.7%)	1.0000	1 (0.2%)	1.0000	-	-
Liver Problems	2 (4.1%)	9 (1.5%)	0.1978	3 (0.7%)	0.0791	0 (0.0%)	1.0000
Lung Problems	1 (2.0%)	4 (0.7%)	0.3246	0 (0.0%)	0.0990	0 (0.0%)	1.0000
Bladder Problems	0 (0.0%)	3 (0.5%)	1.0000	1 (0.2%)	1.0000	-	-

Notes:

[1] Tamoxifen is the reference group.

[2] P-values are calculated using Fisher's exact tests.

[4] Other gastrointentinal symptoms inlcuded taste change, acid reflux, stomach/bowel problems, bloating and esophagus.

[5] Cardiovascular diseases included hypertention, heart palpitation and low blood pressure.

[6] Eye problems included dry eyes, tearing and blurred vision.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

In the anastrozole group, patients experienced significantly more musculoskeletal symptoms compared with those in the tamoxifen group (anastrozole 85.5% vs. tamoxifen 42.9%; $p < 0.0001$). Arthralgia/myalgia was reported more significantly frequently in anastrozole group (78.6% vs. 34.7%; $p < 0.0001$). The incidence of joint stiffness and trigger fingers with anastrozole was statistically significantly higher than with tamoxifen ($p < 0.05$), while the incidence of cramps with anastrozole was significantly lower (2% vs. 14.3%; $p = 0.0002$). 241 cases (40.0%) of nervous system problems were reported in the anastrozole group, compared with 12 cases (24.5%) in the tamoxifen group, and this was statistically significant ($p = 0.0332$). With regard to gynecologic side effects, patients receiving anastrozole had significantly more loss of libido occurrence than those receiving tamoxifen (16.6% vs. 0.0%; $p = 0.0003$). Most of these events were in patients who reported vaginal dryness and dyspareunia. Vaginal discharge/bleeding and other serious gynecologic side effects occurred significantly more often in tamoxifen group ($p < 0.005$). Vasomotor symptoms occurred significantly less often in anastrozole patients than in tamoxifen patients (36.5% vs. 59.2%; $p = 0.0022$), including significantly less hot flashes (34.2% vs. 53.1%; $p = 0.0123$). In addition, compared with the tamoxifen patients, anastrozole patients experienced significantly more sleep disorders (20.4% vs. 4.1%; $p = 0.0038$), less impairment in cognitive function (0.5% vs. 4.1%; $p = 0.048$) and less dyspnea (1.0% vs. 8.2%; $p = 0.0043$).

Letrozole group was associated with significantly increased incidence of musculoskeletal symptoms (letrozole 84.8% vs. tamoxifen 42.9%; $p < 0.0001$). In letrozole group, arthralgia/myalgia was reported more significantly frequently (78.0% vs. 34.7%; $p < 0.0001$), while cramps was reported less frequently (2.2% vs. 14.3%; $p = 0.0006$). Tamoxifen was significantly better tolerated than letrozole with respect to nervous system problems (tamoxifen 24.5% vs. letrozole 43.5%; $p = 0.0139$). In addition, decreased libido was reported more frequently with letrozole than with tamoxifen (letrozole 17.0% vs. tamoxifen 0.0%; $p = 0.0003$), while vaginal discharge/bleeding (0.7% vs. 10.2%) and other serious gynecologic side effects (0.4% vs. 8.2%) were reported less frequently in letrozole group ($p < 0.01$). In terms of vasomotor symptoms, they occurred significantly less often in patients receiving letrozole than those receiving tamoxifen (30.7% vs. 59.2%; $p = 0.0001$). Furthermore,

letrozole users experienced significantly more sleep disorders (21.7% vs. 4.1%; p = 0.0021), and alopecia (18.8% vs. 6.1%; p = 0.028), and significantly less dyspnea (1.1% vs. 8.2%; p = 0.0074).

Exemestane also resulted in significantly more musculoskeletal symptoms than tamoxifen (exemestane 70.8% vs. tamoxifen 42.9%; p = 0.0282). In exemestane group, arthralgia/myalgia and trigger fingers were reported more significantly frequently (62.5% vs. 34.7% for arthralgia/myalgia; 12.5% vs. 0.0% for trigger fingers; $p < 0.05$). The frequency of nervous system problems was reported significantly higher in exemestane group (62.5% vs. 24.5%; p = 0.0022), including more significant carpal tunnel syndrome (33.3% vs. 2.0%; p = 0.0004) and neuropathy (54.2% vs. 20.4%; p = 0.0065). Furthermore, exemestane was significantly better tolerated than tamoxifen with regard to vasomotor symptoms (16.7% vs. 59.2%; p = 0.0009), including significantly less hot flashes (12.5% vs. 53.1%; p = 0.0009). While tamoxifen was significantly better tolerated than exemestane regarding sleep disorders (tamoxifen 29.2% vs. exemestane 4.1%; p = 0.0046).

3.5.2.2 Multivariate Analysis

The incidence and likelihood of developing side effects for postmenopausal breast cancer patients treated with tamoxifen and each AI during the first three months were compared by using univariate and multivariate regression models. Tamoxifen patients were the reference group. Age, duration of hormonal medication, concurrent drug use, and prior drug use were controlled for the analysis. The results of comparison between tamoxifen and anastrozole/letrozole/exemestane will be presented separately. An IRR > 1 indicated that AIs patients had higher incidence of incurring one side effect than tamoxifen patients, while an OR > 1 indicated that AIs patients had a higher probability of experiencing one side effect compared to tamoxifen patients.

a) Anastrozole vs. Tamoxifen

Table 22 shows that after controlling for the different confounding factors, patients receiving anastrozole were associated with a significant increase in the musculoskeletal symptoms incidence rate than those receiving tamoxifen (adjusted IRR 2.14 [1.37 - 3.36], p = 0.0009; adjusted OR 12.12 [6.19 - 23.74], p < 0.0001). Patients in anastrozole group reported significantly more pain symptoms than those in tamoxifen group (adjusted IRR 2.25 [1.55 - 4.21], p = 0.0002; adjusted OR 11.68 [5.99 - 22.80], p < 0.0001). Compared with tamoxifen patients, anastrozole patients had higher probability of developing arthralgia or myalgia (adjusted OR 9.80 [5.04 - 19.06]; p < 0.0001), stiff joint (adjusted OR 8.20 [1.11 - 60.71]; p = 0.0393), while they had lower probability of developing cramps group (adjusted OR 0.10 [0.04 - 0.28]; p < 0.0001). The incidence of nervous system problems was also significantly higher in anastrozole group (adjusted OR 2.20 [1.11 - 4.36]; p = 0.0243). Regarding gynecologic side effects, patients receiving anastrozole had a greater risk of vaginal dryness (adjusted OR 1.64 [0.56 - 4.80]; p = 0.3647), whereas they had a significantly lower risk of vaginal discharge/bleeding (adjusted OR 0.16 [0.05 - 0.53]; p = 0.0025) and other serious gynecologic side effects (adjusted OR 0.07 [0.01 - 0.35]; p = 0.0011). In addition, tamoxifen patients were more likely to develop vasomotor symptoms, especially hot flashes (adjusted OR 0.55 [0.30 - 1.00]; p = 0.049). Furthermore, patients receiving anastrozole were also associated with significantly increased occurrence of sleep disorders with an OR of 5.98 (p = 0.0145), and significantly decreased incidence rate of cognitive difficulty with an OR of 0.15 (p = 0.0468), and dyspnea with an OR of 0.13 (p = 0.0033).

Table 22: Comparison of Side Effects Reported by Breast Cancer Patients

Anastrozole vs. Tamoxifen

Side Effects	Tamoxifen N=49	Anastrozole N=602						Anastrozole N=602					
		Univariate			Multivariate [1]			Univariate			Multivariate [1]		
		IRR (95% CI)	P - Value		IRR (95% CI)	P - Value		OR (95% CI)	P - Value		OR (95% CI)	P - Value	
Musculoskeletal Symptoms	*Reference Group*	2.00 (1.29 - 3.09)	0.0019	**	2.14 (1.37 - 3.36)	0.0009	**	7.89 (4.29 - 14.52)	<.0001	**	12.12 (6.19 - 23.74)	<.0001	**
Pain		2.36 (1.46 - 3.83)	0.0005	**	2.55 (1.55 - 4.21)	0.0002	**	8.51 (4.56 - 15.89)	<.0001	**	11.68 (5.99 - 22.80)	<.0001	**
Arthralgia/Myalgia		2.26 (1.40 - 3.67)	0.0009	**	2.47 (1.50 - 4.08)	0.0004	**	6.90 (3.71 - 12.83)	<.0001	**	9.80 (5.04 - 19.06)	<.0001	**
Bone Pain		2.03 (0.64 - 6.45)	0.2276		2.04 (0.64 - 6.49)	0.2291		2.18 (0.66 - 7.19)	0.1997		2.19 (0.66 - 7.28)	0.2000	
Joint-Stiffness		6.51 (0.91 - 46.79)	0.0626		7.09 (0.98 - 51.16)	0.0521		7.36 (1.00 - 54.04)	0.0498	*	8.20 (1.11 - 60.71)	0.0393	*
Cramps		0.14 (0.05 - 0.35)	<.0001	**	0.12 (0.05 - 0.32)	<.0001	**	0.12 (0.05 - 0.33)	<.0001	**	0.10 (0.04 - 0.28)	<.0001	**
Nervous System Problems		1.63 (0.92 - 2.92)	0.0966		1.68 (0.94 - 3.01)	0.0815		2.06 (1.05 - 4.03)	0.0350	*	2.20 (1.11 - 4.36)	0.0243	*
Headache		1.71 (0.41 - 7.06)	0.4589		1.74 (0.42 - 7.23)	0.4491		1.76 (0.41 - 7.51)	0.4435		1.80 (0.42 - 7.76)	0.4322	
Carpal Tunnel Syndrome		5.13 (0.71 - 36.97)	0.1048		5.23 (0.72 - 37.82)	0.1013		5.61 (0.76 - 41.35)	0.0906		5.81 (0.78 - 43.10)	0.0853	
Neuropathy		1.44 (0.76 - 2.72)	0.2613		1.55 (0.56 - 4.31)	0.3964		1.62 (0.79 - 3.33)	0.1846		1.66 (0.80 - 3.44)	0.1739	
Gynecologic Side Effects													
Vaginal Dryness		1.36 (0.50 - 3.74)	0.5470		1.55 (0.56 - 4.31)	0.3964		1.41 (0.49 - 4.04)	0.5237		1.64 (0.56 - 4.80)	0.3647	
Vaginal Discharge/Bleeding		0.15 (0.05 - 0.44)	0.0006	**	0.18 (0.06 - 0.56)	0.0030	**	0.13 (0.04 - 0.42)	0.0005	**	0.16 (0.05 - 0.53)	0.0025	**
Other Serious Side Effects		0.06 (0.01 - 0.27)	0.0003	**	0.08 (0.02 - 0.37)	0.0014	**	0.06 (0.01 - 0.26)	0.0002	**	0.07 (0.01 - 0.35)	0.0011	**
Vasomotor Symptoms		0.62 (0.42 - 0.91)	0.0147	*	0.68 (0.46 - 1.02)	0.0593		0.40 (0.22 - 0.72)	0.0023	**	0.46 (0.25 - 0.85)	0.0132	*
Hot Flashes		0.64 (0.43 - 0.97)	0.0351	*	0.72 (0.47 - 1.10)	0.1286		0.46 (0.26 - 0.83)	0.0094	**	0.55 (0.30 - 1.00)	0.0490	*
Sweats		0.49 (0.22 - 1.09)	0.0792		0.56 (0.24 - 1.26)	0.1584		0.45 (0.19 - 1.06)	0.0686		0.51 (0.21 - 1.24)	0.1385	
Sleep Disorders		5.01 (1.24 - 20.24)	0.0239	*	4.94 (1.22 - 20.04)	0.0254	*	6.03 (1.45 - 25.19)	0.0137	*	5.98 (1.42 - 25.10)	0.0145	*
Cogitive Difficulty		0.12 (0.02 - 0.73)	0.0212	*	0.16 (0.03 - 0.99)	0.0486	*	0.12 (0.02 - 0.72)	0.0208	*	0.15 (0.02 - 0.97)	0.0468	*
Dyspnea		0.12 (0.03 - 0.43)	0.0011	**	0.14 (0.04 - 0.53)	0.0037	**	0.11 (0.03 - 0.42)	0.0010	**	0.13 (0.03 - 0.51)	0.0033	**

Notes:

[1] Adjusted differences were estimated from multivariate regression models controlling for age, duration of hormonal medication, concurrent drug use, and prior drug use.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

CI: Confidence Intervals

b) Letrozole vs. Tamoxifen

After adjustment for age, duration of hormonal medication, concurrent drug use and prior drug use, Table 23 presents that compared with patients in tamoxifen group, patients in letrozole group were associated with a significantly higher musculoskeletal symptoms incidence rate (adjusted IRR 2.05 [1.31 - 3.23], p = 0.0018; adjusted OR 8.60 [4.46 - 16.59], p < 0.0001), especially arthralgia or myalgia (adjusted IRR 2.33 [1.41 - 3.86], p = 0.001; adjusted OR 7.37 [3.81 - 14.25], p < 0.0001). However, patients in tamoxifen group more easily experienced cramps (adjusted IRR 0.17 [0.06 - 0.46]; p = 0.0005; adjusted OR 0.15 [0.05 - 0.42]; p = 0.0003). Similar to anastrozole, letrozole was also associated with a significantly increased incidence rate of nervous system problems at the three-month follow-up visit (adjusted OR 2.27 [1.13 - 4.56]; p = 0.0208). Additionally, letrozole patients had a higher risk of developing vaginal dryness with an OR of 2.74 (p = 0.0796), and significantly lower risk of developing vaginal discharge/bleeding (adjusted OR 0.06 [0.01 - 0.27]; p = 0.0002) and other serious gynecologic side effects (adjusted OR 0.05 [0.01 - 0.29]; p = 0.0008). With respect to vasomotor symptoms, letrozole users less easily experienced them than tamoxifen users with an IRR of 0.53 (p = 0.0026). The risk of hot flashes was higher in tamoxifen group (adjusted OR 0.32 [0.18 - 0.60]; p = 0.0004), so did the sweats (adjusted OR 0.68 [0.28 - 1.66]; p = 0.3974). Furthermore, letrozole group had higher probability of developing sleep disorders (adjusted OR 6.52 [1.54 - 27.59]; p = 0.0109) and alopecia (adjusted OR 3.20 [0.96 - 10.71]; p = 0.0588). Oppositely, letrozole users had lower probability of developing dyspnea (adjusted OR 0.11 [0.03 - 0.49]; p = 0.0034).

Table 23: Comparison of Side Effects Reported by Breast Cancer Patients

Letrozole vs. Tamoxifen

Side Effects	Tamoxifen N=49	Letrozole N=446						Letrozole N=446					
		Univariate			Multivariate [1]			Univariate			Multivariate [1]		
		IRR (95% CI)	P - Value		IRR (95% CI)	P - Value		OR (95% CI)	P - Value		OR (95% CI)	P - Value	
Musculoskeletal Symptoms	*Reference Group*	1.98 (1.27 - 3.07)	0.0024	**	2.05 (1.31 - 3.23)	0.0018	**	7.41 (3.98 - 13.80)	<.0001	**	8.60 (4.46 - 16.59)	<.0001	**
Pain		2.34 (1.44 - 3.81)	0.0006	**	2.44 (1.47 - 4.04)	0.0005	**	8.11 (4.30 - 15.30)	<.0001	**	8.90 (4.59 - 17.23)	<.0001	**
Arthralgia/Myalgia		2.25 (1.38 - 3.66)	0.0011	**	2.33 (1.41 - 3.86)	0.0010	**	6.68 (3.56 - 12.54)	<.0001	**	7.37 (3.81 - 14.25)	<.0001	**
Bone pain		2.09 (0.65 - 6.67)	0.2141		2.15 (0.65 - 7.09)	0.2072		2.25 (0.68 - 7.46)	0.1863		2.30 (0.66 - 8.07)	0.1935	
Joint-Stiffness		4.72 (0.65 - 34.31)	0.1248		5.33 (0.73 - 39.00)	0.0995		5.12 (0.69 - 38.04)	0.1103		5.95 (0.79 - 44.91)	0.0836	
Cramps		0.16 (0.06 - 0.41)	0.0002	**	0.17 (0.06 - 0.46)	0.0005	**	0.14 (0.05 - 0.38)	0.0001	**	0.15 (0.05 - 0.42)	0.0003	**
Nervous System Problems		1.78 (0.99 - 3.18)	0.0535		1.70 (0.94 - 3.05)	0.0783		2.37 (1.21 - 4.67)	0.0124	*	2.27 (1.13 - 4.56)	0.0208	*
Headache		1.81 (0.43 - 7.55)	0.4140		1.67 (0.39 - 7.15)	0.4871		1.88 (0.44 - 8.08)	0.3973		1.74 (0.39 - 7.78)	0.4686	
Carpal Tunnel Syndrome		4.72 (0.65 - 34.31)	0.1248		5.14 (0.70 - 37.51)	0.1068		5.12 (0.69 - 38.04)	0.1103		5.75 (0.76 - 43.24)	0.0894	
Neuropathy		1.64 (0.86 - 3.11)	0.1314		1.58 (0.83 - 3.02)	0.1628		1.96 (0.95 - 4.03)	0.0685		1.91 (0.91 - 3.99)	0.0870	
Gynecologic Side Effects													
Vaginal Dryness		2.22 (0.82 - 6.07)	0.1185		2.47 (0.87 - 7.01)	0.0887		2.50 (0.87 - 7.14)	0.0878		2.74 (0.89 - 8.43)	0.0796	
Vaginal Discharge/Bleeding		0.07 (0.02 - 0.28)	0.0002	**	0.07 (0.02 - 0.29)	0.0003	**	0.06 (0.01 - 0.26)	0.0002	**	0.06 (0.01 - 0.27)	0.0002	**
Other Serious Side Effects		0.05 (0.01 - 0.30)	0.0008	**	0.06 (0.01 - 0.31)	0.0009	**	0.05 (0.01 - 0.28)	0.0007	**	0.05 (0.01 - 0.29)	0.0008	**
Vasomotor Symptoms		0.52 (0.35 - 0.77)	0.0013	**	0.53 (0.35 - 0.80)	0.0026	**	0.31 (0.17 - 0.56)	0.0001	**	0.31 (0.17 - 0.58)	0.0002	**
Hot Flashes		0.50 (0.33 - 0.76)	0.0013	**	0.51 (0.33 - 0.79)	0.0025	**	0.32 (0.17 - 0.58)	0.0002	**	0.32 (0.18 - 0.60)	0.0004	**
Sweats		0.66 (0.30 - 1.47)	0.3074		0.72 (0.32 - 1.63)	0.4267		0.62 (0.26 - 1.48)	0.2826		0.68 (0.28 - 1.66)	0.3974	
Sleep Disorders		5.33 (1.31 - 21.61)	0.0192	*	5.27 (1.29 - 21.49)	0.0204	*	6.53 (1.56 - 27.37)	0.0103	*	6.52 (1.54 - 27.59)	0.0109	*
Dyspnea		0.14 (0.04 - 0.51)	0.0031	**	0.13 (0.03 - 0.51)	0.0037	**	0.13 (0.03 - 0.49)	0.0028	**	0.11 (0.03 - 0.49)	0.0034	**
Alopecia		3.08 (0.97 - 9.73)	0.0558		2.74 (0.87 - 8.71)	0.0864		3.56 (1.08 - 11.72)	0.0369	*	3.20 (0.96 - 10.71)	0.0588	

Notes:

[1] Adjusted differences were estimated from multivariate regression models controlling for age, duration of hormonal medication, concurrent drug use, and prior drug use.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

CI: Confidence Intervals

c) Exemestane vs. Tamoxifen

In Table 24, exemestane patients reported significantly more musculoskeletal symptoms at the three-month follow-up visit than tamoxifen patients (adjusted OR 3.54 [1.09 - 11.52]; p = 0.0355) after adjustment for all other characteristics. Patients in exemestane group more easily developed pain, especially arthralgia or myalgia (adjusted OR 3.54 [1.10 - 11.45]; p = 0.0344). The result of bone pain did not change after adjusting for established risk factors, even though the risk of developing was higher in exemestane group. Compared with tamoxifen patients, exemestane patients had a significant increase in nervous system problems incidence rate (adjusted OR 4.22 [1.29 - 13.83]; p = 0.0173). Patients receiving exemestane were associated with a significant higher risk of carpal tunnel syndrome with an OR of 15.76 (p = 0.0163), and neuropathy with an OR of 3.77 (p = 0.0309). The probability of developing headache was higher in exemestane as well with an OR of 1.13, but it was not statistically significant (p = 0.9284). Similar to anastrozole and letrozole, exemestane was also associated with a significantly decreased incidence rate of vasomotor symptoms compared with tamoxifen (adjusted IRR 0.32 [0.10 - 0.98]; p = 0.0459; adjusted OR 0.17 [0.04 - 0.62]; p = 0.0079). Tamoxifen resulted in a significant higher incidence rate of hot flashes (adjusted OR 0.17 [0.04 - 070]; p = 0.0145). However, there was non-significant difference of night sweats between the two groups, even though the risk was higher in tamoxifen patients. Additionally, it was observed that sleep disorders was more easily to develop in exemestane patients with an IRR of 7.61 (p = 0.0294) and an OR of 12.92 (p = 0.0156) than that in tamoxifen patients.

Table 24: Comparison of Side Effects Reported by Breast Cancer Patients

Exemestane vs. Tamoxifen

Side Effects	Tamoxifen N=49	Exemestane N=24						Exemestane N=24					
		Univariate			Multivariate [1]			Univariate			Multivariate [1]		
		IRR (95% CI)	P - Value		IRR (95% CI)	P - Value		OR (95% CI)	P - Value		OR (95% CI)	P - Value	
Musculoskeletal Symptoms	*Reference Group*	1.65 (0.87 - 3.13)	0.1235		1.72 (0.83 - 3.56)	0.1436		3.24 (1.14 - 9.22)	0.0277	*	3.54 (1.09 - 11.52)	0.0355	*
Pain		1.92 (0.97 - 3.80)	0.0608		2.08 (0.96 - 4.53)	0.0642		3.76 (1.34 - 10.57)	0.0119	*	4.66 (1.39 - 15.59)	0.0124	*
Arthralgia/Myalgia		1.80 (0.90 - 3.61)	0.0966		1.89 (0.85 - 4.18)	0.1176		3.14 (1.14 - 8.65)	0.0272	*	3.54 (1.10 - 11.45)	0.0344	*
Bone pain		2.04 (0.41 - 10.12)	0.3820		2.63 (0.44 - 15.57)	0.2874		2.19 (0.41 - 11.77)	0.3607		2.94 (0.44 - 19.73)	0.2665	
Nervous System Problems		2.55 (1.19 - 5.45)	0.0156	*	2.16 (0.91 - 5.13)	0.0818		5.14 (1.79 - 14.72)	0.0023	**	4.22 (1.29 - 13.83)	0.0173	*
Headache		2.04 (0.29 - 14.49)	0.4754		1.18 (0.12 - 11.20)	0.8871		2.14 (0.28 - 16.17)	0.4624		1.13 (0.08 - 15.42)	0.9284	
Carpal Tunnel Syndrome		16.33 (2.04 - 130.59)	0.0085	**	11.14 (1.24 - 100.04)	0.0314	*	24.00 (2.78 - 206.96)	0.0038	**	15.76 (1.66 - 149.54)	0.0163	*
Neuropathy		2.65 (1.16 - 6.05)	0.0203	*	2.21 (0.86 - 5.66)	0.0997		4.61 (1.59 - 13.33)	0.0048	**	3.77 (1.13 - 12.60)	0.0309	*
Vasomotor Symptoms		0.28 (0.10 - 0.80)	0.0175	*	0.32 (0.10 - 0.98)	0.0459	*	0.14 (0.04 - 0.47)	0.0014	**	0.17 (0.04 - 0.62)	0.0079	**
Hot Flashes		0.24 (0.07 - 0.78)	0.0177	*	0.29 (0.08 - 1.02)	0.0542		0.13 (0.03 - 0.48)	0.0024	**	0.17 (0.04 - 0.70)	0.0145	*
Sweats		0.58 (0.12 - 2.81)	0.5014		1.00 (0.15 - 6.49)	0.9976		0.55 (0.10 - 2.85)	0.4726		1.01 (0.13 - 7.76)	0.9950	
Sleep Disorders		7.15 (1.48 - 34.40)	0.0142	*	7.61 (1.22 - 47.28)	0.0294	*	9.68 (1.83 - 51.22)	0.0076	**	12.92 (1.62 - 102.79)	0.0156	*

Notes:

[1] Adjusted differences were estimated from multivariate regression models controlling for age, duration of hormonal medication, concurrent drug use, and prior drug use.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

CI: Confidence Intervals

3.5.3 Comparison of Satisfaction

The satisfaction information was determined by the rating of medication, which used a five-point scale (1 "dissatisfied", 2 "not satisfied", 3 "somewhat satisfied", 4 "satisfied", and 5 "very satisfied"). The specific ratings for each of the four cohorts were listed in Figure 9.

Figure 9: Overall Patient Satisfaction with Hormonal Medications

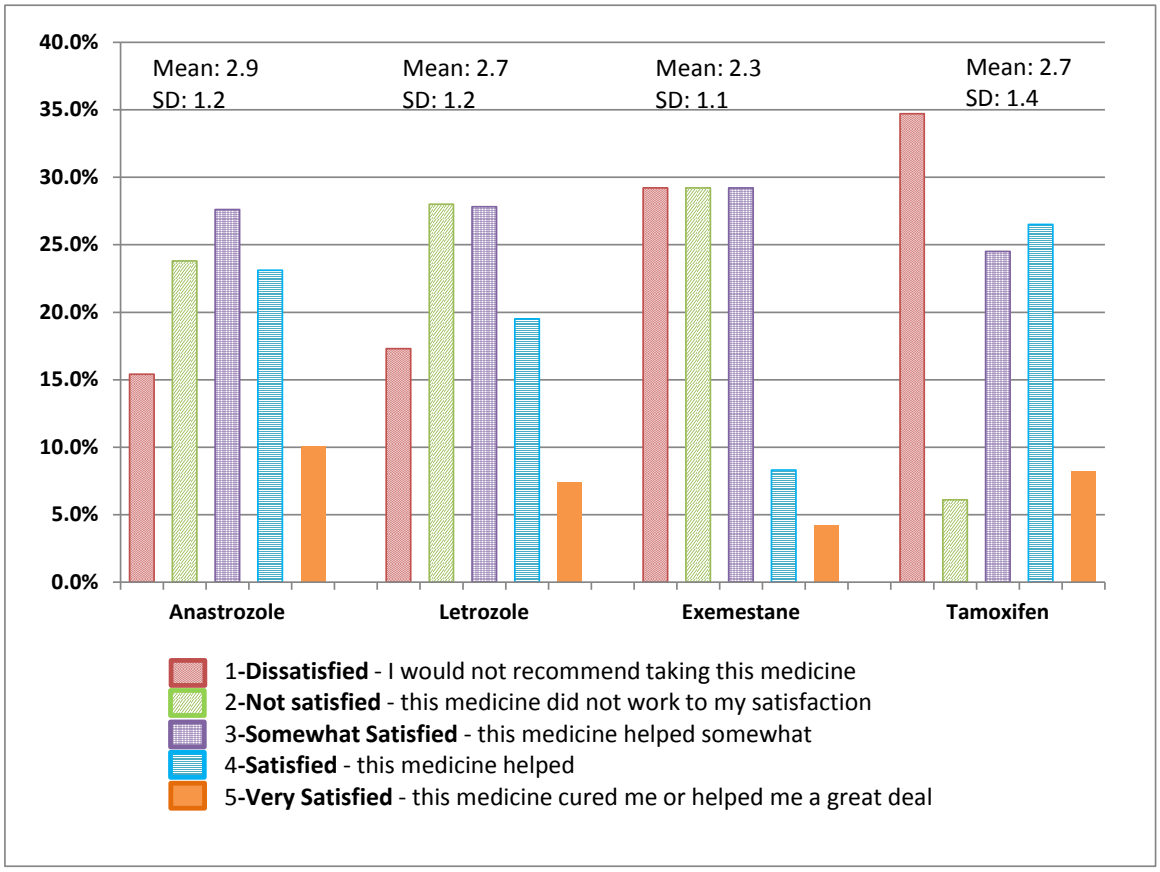


Figure 9 shows that anastrozole had the highest mean rating (2.9 out of 5, close to satisfaction) followed by letrozole and tamoxifen (2.7 out of 5, close to satisfaction), while exemestane had the lowest mean drug rating (2.3 out of 5, not satisfied). Anastrozole and tamoxifen had relatively high percentage of rating "very satisfied" (10.1% for anastrozole, 8.2% for tamoxifen). Tamoxifen also had the highest

percentage of patients who rated the drug as dissatisfaction. For all four cohorts, most of the patients rated their satisfaction score 3 (somewhat satisfaction).

As presented in Table 25, side effect was a major reason affecting patient satisfaction. 99% patients explicitly reported that they experienced at least one side effect. Patients who reported side effects rated their drugs significantly lower than patients who reported not experiencing any side effect ($p < 0.05$). Compared with tamoxifen patients, more patients receiving AIs reported at least one side effect (93.9% for tamoxifen vs. 99.2% for anastrozole, 99.3% for letrozole, and 100% for exemestane, respectively). Few patients with AIs therapy reported no side effects; the percentage was less than 1%. It was noted that the rating of exemestane was the lowest, and all exemestane patients experienced side effects. Although tamoxifen had the lowest percentage of patients who reported more than one side effect, it had the highest percentage of patients who explicitly reported no side effect (6.1%).

Table 25: Mean Satisfaction for Patients Reporting ⩾ 1 Side Effects Compared to Patients Reporting No Side Effect

Drug Class	Number of Patients	Patients Reporting ≥1 Side Effects			Patients Explicitly Reporting No Side Effect			P-Value	
		N(%)	Mean Rating	SD	N(%)	Mean Rating	SD		
Anastrozole	602	597 (99.2%)	2.9	1.2	5 (0.8%)	5.0	0.0	<.0001	**
Letrozole	446	443 (99.3%)	2.7	1.2	3 (0.7%)	4.7	0.6	0.0250	*
Exemestane	24	24 (100%)	2.3	1.1	-	-	-	-	
Tamoxifen	49	46 (93.9%)	2.6	1.4	3 (6.1%)	4.3	0.6	0.0124	*
Total	1,121	1,110 (99.0%)	2.8	1.2	11 (1.0%)	4.7	0.5	<.0001	**

Notes:
** $p < 0.01$ and * $p < 0.05$ for the test of the null hypothesis of equality of means ratings between patients with and without side effects.
SD: Standard Deviation

For all hormonal medications, musculoskeletal symptoms, nervous system problems, vasomotor symptoms, sleep disorders and gynecologic side effects significantly negatively impacted patients' rating compared with patients who reported no side effects. See Table 26.

Table 26: Mean Satisfaction for Patients Reporting Most Common Side Effects Compared to Patients Reporting No Side Effect

Drug Class	Musculoskeletal Symptoms			Nervous System Problems			Vasomotor Symptoms			Sleep Disorders			Gynecologic Side Effects			Patients Explicitly Reporting No Side Effect	
	Mean Rating	SD		Mean Rating	SD		Mean Rating	SD		Mean Rating	SD		Mean Rating	SD		Mean Rating	SD
Anastrozole	2.8	1.2	**	2.6	1.1	**	2.9	1.1	**	2.6	1.1	**	2.7	1.1	**	5.0	0.0
Letrozole	2.6	1.1	*	2.5	1.1	*	2.6	1.1	*	2.5	1.1	*	2.8	1.2	*	4.7	0.6
Exemestane	2.2	1.0		2.4	1.3		2.0	0.8		2.0	1.2		2.0	1.4		-	-
Tamoxifen	2.5	1.4	**	2.0	1.1	**	2.5	1.4	**	3.5	2.1		2.2	1.3	**	4.3	0.6

Notes:

** $p < 0.01$ and * $p < 0.05$ for the test of the null hypothesis of equality of means ratings between patients with and without side effects.

SD: Standard Deviation

The mean satisfaction drug-rating for anastrozole patients reporting no side effect was 5.0, which was much higher than that for them reporting musculoskeletal symptoms (2.8), nervous system problems (2.6), vasomotor symptoms (2.9), sleep disorders (2.6), or gynecologic side effects (2.7). The same trend was found for letrozole and tamoxifen patients, the difference of drug-rating is almost two scores. For exemestane patients, all patients reported at least one side effect. The mean drug-rating for patients reporting one of the above side effects was between 2.0 and 2.4. It meant that they were not satisfied with exemestane.

3.5.3.1 Comparison between Satisfaction and Non-Satisfaction

Table 27 presents the outcome of comparing the likelihood of being satisfied for patients treated with tamoxifen with patients treated with each AI. Drug rating ≥ 3 indicated satisfaction.

After controlling for the different confounding factors (i.e., age, duration of medication, medication history, currently taking medication status and some side effects), anastrozole patients had higher probability of feeling satisfied than tamoxifen patients (adjusted OR 2.37 [1.10 - 5.09]; $p = 0.0267$). In univariate analysis, letrozole patients had lower probability of feeling satisfied than tamoxifen patients. Despite that

the regression-adjusted probability of letrozole patients feeling satisfied was 1.47 times higher than that of tamoxifen patients; the difference was not statistically significant (p = 0.3278). Moreover, the adjusted OR 0.51 suggested that the probability of satisfaction was 0.51 times less likely to occur in exemestane patients compared with tamoxifen patients. However, this difference was not significant (p = 0.3918).

Table 27: Comparison between Satisfaction and Non-Satisfaction[1]

Binary Logistic Regression

	Tamoxifen N=49	Anastrozole [2] N=602		Letrozole [3] N=446		Exemestane [2] N=24	
		OR (95% CI)	P - Value	OR (95% CI)	P - Value	OR (95% CI)	P - Value
Univariate Analysis	*Reference Group*	1.07 (0.59-1.93)	0.8240	0.83 (0.46-1.52)	0.5503	0.49 (0.18-1.33)	0.1616
Multivariate Analysis		2.37 (1.10-5.09)	0.0267 *	1.47 (0.68-3.15)	0.3278	0.51 (0.11-2.40)	0.3918

Notes:

[1] Drug rating ≥ 3 were considered satisfaction.

[2] The multivariate logistic regression for anastrozole and exemestane were adjusted for age, duration of hormonal medication, concurrent drug use, prior drug use, currently taking medication status, musculoskeletal symptoms, nervous system problems, vasomotor symptoms, gynecology side effects, and sleep disorders.

[3] The multivariate logistic regression for letrozole was adjusted for age, duration of hormonal medication, concurrent drug use, prior drug use, currently taking medication status, musculoskeletal symptoms, nervous system problems, vasomotor symptoms, gynecology side effects, sleep disorders and dermatology side effects.

** p-value significant at α = 0.01; * p-value significant at α = 0.05.

Table 28.1 - 28.3 summarize outcomes of the factors affecting satisfaction rating of patients treated with tamoxifen in comparison to patients treated with each AI. Tamoxifen group was the reference group.

As shown in Table 28.1, the probability to be satisfied was associated with longer duration of medication (OR = 1.03; p < 0.0001), currently no medication withdrawal (OR = 4.20; p < 0.0001), younger age (OR = 0.96; p = 0.0023), less musculoskeletal symptoms (OR = 0.39; p = 0.0008), less nervous system problems (OR = 0.68; p = 0.0354), and less sleep disorders (OR = 0.58; p = 0.0174). Although concurrent drug use, vasomotor symptoms caused the probability of being satisfied to increase, the differences were not recorded.

Table 28.1: Factors affecting on Satisfaction Rating - Anastrozole vs. Tamoxifen Satisfaction vs. Non-Satisfaction

Analysis of Parameter Estimate							
Parameter	**Estimate**	**SE**	**OR**	**95% CI**		**P-Value**	
Age	-0.0387	0.0127	0.96	-0.0635	-0.0138	0.0023	**
Duration	0.0267	0.0055	1.03	0.0160	0.0374	<.0001	**
Prior Drug Use	-0.2300	0.2329	0.79	-0.6865	0.2265	0.3234	
Concurrent Drug Use	0.3899	0.5060	1.48	-0.6019	1.3816	0.4410	
Currently Consistent Use of Medication	1.4358	0.1919	4.20	1.0596	1.8120	<.0001	**
Musculoskeletal Symptoms	-0.9290	0.2785	0.39	-1.4748	-0.3832	0.0008	**
Nervous System Problems	-0.3877	0.1843	0.68	-0.7489	-0.0264	0.0354	*
Vasomotor Symptoms	0.2143	0.1900	1.24	-0.1580	0.5867	0.2592	
Gynecologic Side Effects	-0.2752	0.2142	0.76	-0.6950	0.1446	0.1988	
Sleep Disorders	-0.5400	0.2271	0.58	-0.9851	-0.0949	0.0174	*

Notes:

SE: Standard Error; CI: Confidence Intervals.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Table 28.2: Factors affecting on Satisfaction Rating - Letrozole vs. Tamoxifen Satisfaction vs. Non-Satisfaction

Analysis of Parameter Estimate							
Parameter	**Estimate**	**SE**	**OR**	**95% CI**		**P-Value**	
Age	-0.0127	0.0147	0.99	-0.0415	0.0162	0.3893	
Duration	0.0269	0.0066	1.03	0.0140	0.0399	<.0001	**
Prior Drug Use	0.1988	0.2230	1.22	-0.2383	0.6358	0.3727	
Concurrent Drug Use	0.2790	0.7681	1.32	-1.2265	1.7845	0.7164	
Currently Consistent Use of Medication	1.6861	0.2358	5.40	1.2239	2.1483	<.0001	**
Musculoskeletal Symptoms	-0.5716	0.2796	0.56	-1.1197	-0.0235	0.0410	*
Nervous System Problems	-0.5397	0.2117	0.58	-0.9546	-0.1249	0.0108	*
Vasomotor Symptoms	-0.4081	0.2231	0.66	-0.8454	0.0293	0.0674	
Gynecologic Side Effects	-0.0230	0.2367	0.98	-0.4869	0.4409	0.9224	
Sleep Disorders	-0.3519	0.2630	0.70	-0.8674	0.1636	0.1810	
Dermatology Side Effects	-0.0092	0.2584	0.99	-0.5157	0.4973	0.9716	

Notes:

SE: Standard Error; CI: Confidence Intervals.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Table 28.2 shows that longer duration of medication and currently consistent use of medication caused the rating of satisfaction to increase (OR = 1.03 for duration, OR = 5.40 for currently consistent use of medication; $p < 0.0001$). Musculoskeletal

symptoms and nervous system problems caused probability of being satisfied to decrease (OR = 0.56 for musculoskeletal symptoms, OR = 0.58 for nervous system problems; $p < 0.05$).

Table 28.3: Factors affecting on Satisfaction Rating - Exemestane vs. Tamoxifen Satisfaction vs. Non-Satisfaction

Analysis of Parameter Estimate							
Parameter	**Estimate**	**SE**	**OR**	**95% CI**		**P-Value**	
Age	-0.0519	0.0404	0.95	-0.1311	0.0273	0.1993	
Duration	-0.0050	0.0115	1.00	-0.0276	0.0177	0.6667	
Prior Drug Use	0.3393	0.7023	1.40	-1.0372	1.7159	0.6290	
Concurrent Drug Use	24.8373	-	-	-	-	0.9999	
Currently Consistent Use of Medication	1.6390	0.6281	5.15	0.4080	2.8700	0.0091	**
Musculoskeletal Symptoms	-0.3197	0.5921	0.73	-1.4803	0.8409	0.5892	
Nervous System Problems	-0.4660	0.6414	0.63	-1.7231	0.7911	0.4675	
Vasomotor Symptoms	-0.4418	0.6532	0.64	-1.7220	0.8384	0.4988	
Gynecologic Side Effects	-0.3141	0.7626	0.73	-1.8088	1.1806	0.6804	
Sleep Disorders	-0.1160	0.9213	0.89	-1.9217	1.6898	0.8998	

Notes:

SE: Standard Error; CI: Confidence Intervals.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

In Table 28.3, only currently no medication withdrawal is the significant determinant for satisfaction. The probability of satisfaction was 5.15 times more likely to occur if patients currently were still taking medication ($p = 0.0091$).

3.5.3.2 Comparison of Satisfaction Levels

Table 29 shows the outcome of the likelihood of a higher drug-rating in the group of patients treated with tamoxifen compared with patients treated with AIs.

After adjusting for the contributing factors, the likelihood of rating a higher score with anastrozole patients was 3.62 times than with tamoxifen patients ($p < 0.0001$). Compared with tamoxifen patients, the probability of higher drug-rating significantly increased in letrozole patients with odds of 2.17 ($p = 0.0206$). The tendency to a higher drug-rating was decreased by a multiple of 0.50 in exemestane group. However, the difference was not statistically significant.

Table 29: Comparison of Satisfaction Levels [1]

Ordered Logistic Regression

	Tamoxifen N=49	Anastrozole [2] N=602		Letrozole [3] N=446		Exemestane [2] N=24	
		OR (95% CI)	P - Value	OR (95% CI)	P - Value	OR (95% CI)	P - Value
Univariate Analysis	*Reference Group*	1.35 (0.77-2.36)	0.2906	1.06 (0.60-1.87)	0.8470	0.62 (0.26-1.45)	0.2682
Multivariate Analysis		3.62 (1.90-6.91)	<.0001 **	2.17 (1.13-4.20)	0.0206 *	0.50 (0.14-1.78)	0.2825

Notes:

[1] Satisfaction level was a 5-point scale (from 1 "dissatisfied" to 5 "very satisfied").

[2] The multivariate logistic regression for anastrozole and exemestane were adjusted for age, duration of hormonal medication, concurrent drug use, prior drug use, currently taking medication status, musculoskeletal symptoms, nervous system problems, vasomotor symptoms, gynecology side effects, and

[3] The multivariate logistic regression for letrozole was adjusted for age, duration of hormonal medication, concurrent drug use, prior drug use, currently taking medication status, musculoskeletal symptoms, nervous system problems, vasomotor symptoms, gynecology side effects, sleep disorders and

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Table 30.1 - 30.3 summarize the outcomes of the factors affecting the comparison of satisfaction levels between patients treated with tamoxifen and patients treated with each AI. Tamoxifen group was the reference group.

Table 30.1: Factors affecting on Satisfaction Rating - Anastrozole vs. Tamoxifen Satisfaction Levels

Analysis of Parameter Estimate						
Parameter	**Estimate**	**SE**	**OR**	**95% CI**		**P-Value**
Age	-0.0340	0.0101	0.97	-0.0538	-0.0142	0.0008 **
Duration	0.0223	0.0040	1.02	0.0146	0.0301	<.0001 **
Prior Drug Use	0.0014	0.1864	1.00	-0.3639	0.3668	0.9938
Concurrent Drug Use	0.2739	0.3736	1.32	-0.4583	1.0062	0.4634
Currently Consistent Use of Medication	1.1849	0.1508	3.27	0.8894	1.4804	<.0001 **
Musculoskeletal Symptoms	-1.1253	0.2132	0.32	-1.5431	-0.7075	<.0001 **
Nervous System Problems	-0.6091	0.1483	0.54	-0.8997	-0.3185	<.0001 **
Vasomotor Symptoms	0.1424	0.1503	1.15	-0.1521	0.4370	0.3433
Gynecologic Side Effects	-0.4467	0.1683	0.64	-0.7765	-0.1168	0.0080 **
Sleep Disorders	-0.5019	0.1826	0.61	-0.8597	-0.1441	0.0060 **

Notes:

SE: Standard Error; CI: Confidence Intervals.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

As shown in Table 30.1, age, medication condition, side effects were determinants of rating a higher satisfaction score. The likelihood to a higher rating increased by 2%

due to longer duration of medication ($p < 0.0001$) and 227% due to currently consistent use of medication ($p < 0.0001$), while it decreased by 3% due to elder age ($p = 0.0008$), 68% due to musculoskeletal symptoms ($p < 0.0001$), 46% due to nervous system problems ($p < 0.0001$), 36% due to gynecologic side effects ($p = 0.0008$) and 39% due to sleep disorders ($p = 0.006$), respectively. However, even though prior drug use, concurrent drug use and vasomotor symptoms caused the odds of rating a higher score to increase, significant differences were barely recorded.

Table 30.2: Factors affecting on Satisfaction Rating - Letrozole vs. Tamoxifen Satisfaction Levels

Analysis of Parameter Estimate							
Parameter	**Estimate**	**SE**	**OR**	**95% CI**		**P-Value**	
Age	-0.0156	0.0121	0.98	-0.0392	0.0081	0.1963	
Duration	0.0222	0.0051	1.02	0.0123	0.0322	<.0001	**
Prior Drug Use	0.1491	0.1813	1.16	-0.2062	0.5043	0.4108	
Concurrent Drug Use	0.3101	0.5795	1.36	-0.8258	1.4459	0.5926	
Currently Consistent Use of Medication	1.2985	0.1827	3.66	0.9404	1.6566	<.0001	**
Musculoskeletal Symptoms	-0.7335	0.2313	0.48	-1.1869	-0.2802	0.0015	**
Nervous System Problems	-0.5172	0.1737	0.60	-0.8577	-0.1768	0.0029	**
Vasomotor Symptoms	-0.2848	0.1786	0.75	-0.6349	0.0652	0.1107	
Gynecologic Side Effects	-0.1049	0.1889	0.90	-0.4751	0.2653	0.5785	
Sleep Disorders	-0.4080	0.2086	0.66	-0.8169	0.0008	0.0505	
Dermatology Side Effects	-0.0945	0.2061	0.91	-0.4984	0.3094	0.6465	

Notes:

SE: Standard Error; CI: Confidence Intervals.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

Table 30.2 presents that patients were more likely to rate a higher score if they had longer duration of medication (OR = 1.02; $p < 0.0001$) and currently no medication withdrawal (OR = 3.66; $p < 0.0001$). Whereas they are less likely to rate a higher score if they experienced musculoskeletal symptoms (OR = 0.48; $p = 0.0015$), and nervous system problems (OR = 0.60; $p = 0.0029$). Although gynecologic side effects, sleep disorders and dermatology side effects caused the odds of rating a higher score decreased, the differences were not statistically significant.

Table 30.3 shows that concurrent drug use and currently no medication withdrawal were the significant predictors for a higher satisfaction score. Specifically,

the likelihood to rate a higher score significantly increased by concurrent drug use with odds 6.39 (p = 0.0487), and currently no medication withdrawal with odds 5.26 (p = 0.0024).

Table 30.3: Factors affecting on Satisfaction Rating - Exemestane vs. Tamoxifen Satisfaction Levels

Analysis of Parameter Estimate							
Parameter	**Estimate**	**SE**	**OR**	**95% CI**		**P-Value**	
Age	-0.0467	0.0326	0.95	-0.1105	0.0172	0.1519	
Duration	-0.0021	0.0090	1.00	-0.0198	0.0156	0.8194	
Prior Drug Use	0.9427	0.5951	2.57	-0.2237	2.1091	0.1132	
Concurrent Drug Use	1.8552	0.9412	6.39	0.0105	3.6999	0.0487	*
Currently Consistent Use of Medication	1.6598	0.5470	5.26	0.5878	2.7319	0.0024	**
Musculoskeletal Symptoms	-0.2012	0.4790	0.82	-1.1401	0.7377	0.6745	
Nervous System Problems	-0.9348	0.5383	0.39	-1.9898	0.1203	0.0825	
Vasomotor Symptoms	-0.3746	0.5379	0.69	-1.4289	0.6797	0.4862	
Gynecologic Side Effects	-0.9938	0.6440	0.37	-2.2560	0.2685	0.1228	
Sleep Disorders	0.5509	0.7430	1.73	-0.9053	2.0070	0.4584	

Notes:

SE: Standard Error; CI: Confidence Intervals.

** p-value significant at $\alpha = 0.01$; * p-value significant at $\alpha = 0.05$.

3.6 Discussion

This study used patient self-reported data collected through www.askapatient.com to examine the side effects reported by postmenopausal breast cancer patients receiving hormonal medications (tamoxifen, anastrozole, letrozole and exemestane), and examine the impact on patient satisfaction. This section presents the major findings, the limitations, health policy implications and suggestions for future studies.

3.6.1 Major Findings

Firstly, this study assessed and compared the side effects associated with hormonal medications reported by breast cancer patients. As known from several publications, physician-guided symptom assessment is not sufficient to give a full picture of the real side effects produced by hormonal treatments, hence it normally

underestimates the real treatment burden.[134, 144, 145] Usually, physicians or researchers are more interested in severe side effects like bone fractures or thrombosis, than in uncomplicated, non-life-threatening and easy-to-manage symptoms such as insomnia, weight gain or low energy. Nevertheless, these less serious symptoms may also significantly affect the patients' quality of life and satisfaction. On the other side, patients do not always discuss their symptoms with the doctor, possibly because some symptoms may not constantly disturb them, some symptoms are attributed to menopause, or it is an embarrassment to speak about particular symptoms, for example decreased libido, or problems regarding intercourse. It is also possible that they suppose that the doctor may not be interested in these less serious symptoms. Other reasons include the patient perceive that the oncologist is not the correct person to address some symptoms, e.g. gynecologist deals with gynecologic problems, dermatologist deals with dermatologic problems. Hence, the validated HRQoL questionnaires for breast cancer may fail to show the full picture of patients' reported side effects.

This study used data collected from Askapatient website, where patients could share any experiences on medications without being influenced by caregivers or physicians. A majority of the patients (99%) reporting their experience with the use of tamoxifen and AIs underwent significant side effects. Consistent with the findings of previous literature review, the current study also found that patients commonly reported pains, hot flashes, fatigue, while taking tamoxifen or an AI. Statistically significant differences were observed between the tamoxifen and AIs for side effects as well. Similar to the results reported in some studies, compared with the tamoxifen group, significantly more joint/muscle/bone pain,[200] joint stiffness,[160] nervous system problems,[196] vaginal dryness and loss of libido[142, 143] took place in anastrozole group, whereas significantly less vaginal discharge/bleeding,[143, 145] hot flashes,[145] cognitive difficulty[201, 202] occurred. There were no differences of gastrointestinal symptoms[142, 145] or cardiovascular events[200] between the two treatment groups. Patients in the letrozole group experienced significantly severer problems of musculoskeletal symptoms,[203] hair thinning,[204] or sleep difficulty,[148] whereas significantly less vaginal discharge/bleeding and vasomotor symptoms.[203, 205] Aligned with the previous researches, statistically significant differences were reported between patients taking exemestane and patients taking tamoxifen. Exemestane was associated

with significantly more bone/muscle aches, [152, 154] carpal tunnel syndrome,[206] vaginal dryness,[152] decreased libido,[152] and insomnia,[147, 154] but with significantly less nervous system problems,[207, 208] vaginal discharge,[144] hot flashes[144]. In addition, barely difference of mental awareness, mood disorders, or low energy/lethargy, between exemestane and tamoxifen were recorded, in spite of constant complaint. [152, 154]

In addition to the side effects discussed above, the current study also showed that anastrozole has been associated with increased rates of tinnitus, dry mouth and growth of facial hair. Dry eyes and blurred vision incurred more often in letrozole patients. Some other minor side effects, such as nausea, flu-like symptoms, teeth problems and bladder problems were noted in anastrozole and letrozole patients. For tamoxifen, it appeared to cause more dyspnea, edema and urinary tract problems, less sleep disorders than AIs patients. Regarding dyspnea and sleep disorders, tamoxifen was associated with significantly higher frequency of dyspnea than anastrozole and letrozole, and significantly lower frequency of sleep disorders than anastrozole, letrozole and exemestane.

Secondly, this study examined patient satisfaction with hormonal medications. The numerical ratings of the medications' effect indicated that many users found the medications helpful overall, with a positive or middle rating. Among these four cohorts, patients were somewhat satisfied with anastrozole, letrozole and tamoxifen. And anastrozole got the highest level of satisfaction (2.9 out of 5), while exemestane had the lowest drug rating (2.3 out of 5), which meant that patients were least satisfied with it. Letrozole and tamoxifen had the same drug rating (2.7 out of 5). For all four cohorts, most of the patients rated their satisfaction score 3.0 (somewhat satisfaction), because they did not know their drug was effective or not. One key reason was the short time of taking the medication; the other key reason was probably the same side effects with prior medication.

Consistent with literatures, side effects significantly negatively impacted patient satisfaction,[170, 175, 176, 177, 181, 182] especially musculoskeletal symptoms and nervous system problems in this study. Besides the side effects, those who were satisfied tended to be long-term and currently consistent users of medication.[179] However, this study did not fully support the hypothesis 5 - patients with concurrent drug use are

more likely to rate a higher score on satisfaction. Concurrent drug use help relieve some side effects, such as hot flashes, pain, etc. It should be a positive effect associated with satisfaction, which was reported by Brod et al.[182] In the current study, although concurrent drug use caused the probability of being satisfied to increase, the differences were not recorded. The key reason is that only a few respondents reported this information. Hence, future research is needed to examine this factor.

Compared with tamoxifen patients, anastrozole patients had a significantly higher probability of experiencing satisfaction, and they had a significantly stronger likelihood of rating a higher score as well. Besides the above factors mentioned, it was also found that older patients were more likely to rate dissatisfaction. This is contradictory to the findings of Cohen G.[171] One explanation is that most anastrozole patients were in age range 50-59. The median age for women to have their natural menopause onset is 51 years old.[194] The menopausal patients are more likely to rate dissatisfaction in terms of menopausal symptoms and other side effects. In addition, sleep disorders also significantly negatively impacted patient satisfaction.

Letrozole patients only had a significantly stronger likelihood of rating a higher score. Long-term and currently no medication withdrawal had positive effect, while musculoskeletal symptoms or nervous system problems had negative effect.

In this study, exemestane patients had a lower probability of experiencing satisfaction than tamoxifen patients, despite adjusting for the contributing factors. One explanation was the small sample size of exemestane patients resulting in the inconclusive validity of the comparison. The other explanation was the prior drug use. Among the exemestane patients who switched from another drug, almost half number of patients (45.8%) used tamoxifen prior to exemestane, and 33.3% patients took the other AIs prior to exemestane. Patients may feel difficult to tell which drug caused the current side effects. In addition, relatively short duration of treatment could also affect the comparison results. Hence, further research is needed.

Finally, the data revealed that although many users found hormonal medications helpful overall with a positive or middle rating, they did not feel that they participated in treatment decisions. Furthermore, they reported that they had not been warned about

side effects, and they were not aware of some of their side effects rated to the medication until they read these comments. Hence, many patients felt very happy to find this website. Two examples from the comments of the data are shown below:

"I wish I had found this website 4 1/2 years ago. I started having severe joint pain about 6-8 months after starting Arimidex and was complaining to oncologist who said it had nothing to do with the drug. I believed him. He said I had arthritis and when it got a lot worse I went to arthritis specialist who confirmed it. I have been on for 5 years and doctor said OK to quit taking it after next month but after reading this today I am quitting right now and praying my body will recover from these side effects. I searched the internet today to see if current opinion was to quit Arimidex after 5 years or if there was any benefit from additional years on the drug when I found this website. You all are saying the same things I have been saying for 4 1/2 years but I thought it was just me."

"My oncologist doesn't seem to think any of this is from Femera when it is clearly written on the warning pamphlet that came with it……My oncologist had his nurse tell me over the phone that my being so ill was just in my mind. If that was the case why did my blood tests show I needed the boost shots?"

It is important that patients who wish to participate in treatment decisions are well informed about the treatment options and are given sufficient support to evaluate the potential consequences of the decision, including discussion with former patients who have similar experiences with the treatments. As noted by Eysenbach, if patients feel satisfied with the adequacy of information provided, the probability for them to feel happy with their participation in the entire process of making decision is higher,[188] the probability for them to comply with medical treatment to gain a better outcome is higher as well.

3.6.2 Study Strengths and Limitations

Nowadays, various media are available for collecting patient-reported outcomes (PROs), and the Internet is increasingly recognized as an important source of

information. Due to the wide availability and easy access of the Internet, as well as dissatisfaction with the information provided by health care providers, patients are becoming more inclined to turn to it for health information and support. Although there is a noteworthy finding that the quality of cancer information from the Internet is not so bad after all in comparison to other topic areas, research based on web data still has some limitations. The discussions in this section will present what strengths and limitations of this study using Askapatient website data.

Study Strengths

The first strength of this study was certainly that Askapatient website provides high quality information. It is the best resource for patient opinion about drug performance, which was established ten years ago and all the prescription drugs are currently approved by the FDA.

Secondly, Askapatient website is able to assess side effects without the patient being influenced by caregivers, as it was completed independently by the patients without the help of nurses or consulting the doctor. Usually, the toxicities and tolerability of treatments in clinical trial are collected by doctors, nurses and/or the study coordinators. Since this kind of information could differ from those reported by patients, the validated HRQoL questionnaires for breast cancer may fail to show the full picture of patients' real side effects. This study provides additional empirical evidence on the side effects reported by breast cancer patients after taking hormonal medications. For example, anastrozole was associated with increased rates of tinnitus, dry mouth and growth of facial hair. Tamoxifen appeared to cause more dyspnea, edema, and urinary tract problems, but less sleep disorders than AIs patients.

Thirdly, as far as I know, this is the first study to compare breast cancer patients' satisfaction about tamoxifen and AIs. Patient satisfaction is the type of outcome that is studied less frequently than other patient-reported outcomes (PROs), particularly health-related quality of life (HRQoL). Nevertheless, such PROs are very important in the studies of cancer because they reflect patients' treatment-related behaviours, and consequently, it will impact the quality of life in cancer patients. Although the side effect profiles of tamoxifen and AIs varied significantly, there were no important

differences in overall QoL. Hence, the information of patient satisfaction with hormonal medications is very useful for policy makers to manage such medications and optimize health expenditure.

Limitations

Askapatient database is a free discussion space without any medical authority. Any people could share their personal experiences with medications here. Meanwhile, there is no validation of how many entries one single patient may have contributed to the website. Although the reliance on self-reporting may not detract much from the study findings, other limitations should be noted.

Firstly, respondents in this study do not represent a random sample. This website presents patients' reporting only from those who were able to find this site on the Internet and wanted to share their experiences with prescribed drugs. At the same time, the respondents may be motivated to access this website due to unusually negative experiences with these drugs. Additionally, people who use the Internet are more likely to be better educated, younger and above middle class than the general population, although the users of Askapatient are older than average Internet users in the current study. Therefore, respondents in this study could not represent the general users of hormonal therapy medications. Moreover, the results are limited by relying upon the respondents' self-reports, which may potentially bias the results.

Secondly, this study may not assess the prevalence of hormonal medication-related side effects. Respondents may not report their complete experiences encountered during the period of treatment. Some respondents appeared to list all the side effects they experienced, the other mentioned only one or two without indicating if they still experienced other side effects. Furthermore, serious life-threatening side effects, such as cerebrovascular events, thromboembolic events and endometrial cancer, were rarely reported probably due to the physical incapability of self-reporting of the patients over the Internet or the relatively short duration of medication treatment. Therefore, not all of the hormonal medication-related side effects addressed in this study could be found in the previous literature review.

Thirdly, in this study, all the hormonal medications must be taken for at least three months, which may not be sufficient to detect attrition that could occur over longer period of time. Moreover, the small sample size will influence its statistical representation of patients' satisfaction estimates.

3.6.3 Health Policy Implication

Based on the findings from this study, some suggestions for the implication of health policy are provided here. Firstly, this study provides additional empirical evidence on the side effects reported by breast cancer patients after taking hormonal medications. In addition to the serious symptoms commonly reported, uncomplicated, non-life-threatening and easy-to-manage symptoms could be a basis for appropriate management decisions or regulatory reporting of breast cancer hormonal medications as well. Based on the side effects reported by the patients in this study, healthcare researchers and clinicians need to be aware that tamoxifen was associated significantly with higher frequency of dyspnea than anastrozole or letrozole, while AIs were associated with significantly higher frequency of sleep disorders than tamoxifen. In addition, anastrozole has been connected with increased rates of tinnitus, dry mouth and growth of facial hair. Dry eyes and blurred vision incurred with letrozole patients. The clinical implications inferred from the findings could provide an indication of best hormonal medication management. In addition, it could be a reference point for future research and benchmark into clinical practice.

Secondly, satisfaction among hormonal medication users is associated with long-term and currently consistent treatment. For this reason, clinicians could further educate patients about the medications, and reinforce the importance for long-term compliance which is the key to successful management of breast cancer.

Finally, this study showed that some other drugs were taken with hormonal medications at the same time to relieve side effects. One of the most frequently used drugs is bisphosphonates (e.g., Boniva, Fosamax) for treating osteoporosis. Nevertheless, in October 2010, the FDA warned patients and health care providers about the possible risk of atypical thigh bone fracture among patients who take

bisphosphonates.[209] Therefore AIs resulting in bone fracture may need to be reconsidered in the future.

3.6.4 Suggestions for Future Studies

Despite the study limitations, the present findings have policy implications meriting further examination. Additional research is needed in larger population, particularly with longer follow-up period, to fully explore the relationship among medication use, self-reported side effects and patient satisfaction. In this study, the duration of hormonal medications is relatively short, which may not have been sufficient to detect some serious side effects that could occur over longer period. As known from the literature, bone mineral density and cardiovascular disease occurred more frequently with AIs, while cerebrovascular events, thromboembolic events and endometrial cancer occurred more frequently with tamoxifen. These serious life-threatening side effects could also be a significant factor of affecting patient satisfaction. Thus, such side effects remain important issues of concern and need to be monitored and followed up in the further research. Likewise, the findings of current study did not fully support hypothesis 5 - patients with concurrent drug use are more likely to rate a higher score on satisfaction. Concurrent drug use could be a contributing factor of medication satisfaction, and previous literature review also reported that.[178] However, in this study concurrent drug use caused the probability of being satisfied to increase, the differences were not recorded. Moreover, the significant factors identified in current study which impact medication satisfaction are not the only factors that have an effect, and further research is needed to identify additional factors, such as age, education and income level.

In addition, the five-Likert scale drug rating in Askapatient website has not been proved to be psychometrically validated. A more detailed analysis with reliable and validated treatment satisfaction questionnaire for medications is needed.

And the current study compared patient satisfaction rating on tamoxifen with that on each AI. Although anastrozole and letrozole patients showed a significantly higher probability of experiencing satisfaction than tamoxifen patients, further confirmation

of the findings is needed. With regard to the comparison between tamoxifen and exemestane, future research is required. Furthermore, from descriptive statistics about three AIs, anastrozole had higher mean rating than letrozole and exemestane. And exemestane had the lowest mean drug rating. Direct head-to-head comparisons of AIs are also needed in the future.

3.6.5 Conclusion

This study used self-reported data to examine patient satisfaction and subjective experiences of treatment with breast cancer hormonal medications - tamoxifen and AIs (anastrozole, letrozole, exemestane). The results supported the hypotheses showing that in comparison to patients receiving tamoxifen, patients receiving AIs experienced significantly more arthralgia/myalgia, bone events, carpal tunnel syndrome, vaginal dryness, sexual dysfunction and sleep disorders, whereas significantly less hot flashes, night sweats, vaginal discharge/bleeding and other serious gynecologic side effects, such as ovarian cysts. When examining the contributing factors that affect hormonal medication satisfaction, it was clear that the occurrence of side effects was a major issue for breast cancer patients and influenced patient satisfaction. This study showed that side effects, especially musculoskeletal symptoms and nervous system problems, significantly and negatively affected patient satisfaction with hormonal medications. Additionally, long-term and currently consistent uses of medications were also important determinants of medication satisfaction. Compared with tamoxifen patients, anastrozole patients had a significantly higher probability of experiencing satisfaction, and they also had a significantly stronger likelihood of rating a higher score; while letrozole patients only showed a significantly stronger likelihood of rating a higher score. Future research to confirm the current results should use a larger sample, and a prospective methodology. Overall, choice of a hormonal medication should involve not only the effectiveness of an agent but also the subjective effects of medications, such as side effect profile and patient satisfaction. This kind of information could improve communication between patients and care providers regarding possible side effects, and improve the quality of life of patients on hormonal medication therapy as well.

Chapter 4: Conclusion

Nowadays, cancer is one of the leading causes of death in the world. The year 2008 World Cancer Report released by the International Agency for Research on Cancer (IARC) estimates that globally there were over 12 million new cases of cancer diagnosed in 2008, 7 million deaths from cancer.[2] And the incidence of cancer continues to increase; by the year 2030 there will be 27 million incident cases of cancer and 17 million cancer deaths.[2] Due to the improved treatments, cancer survival rates have greatly increased in the past few decades. In particular, cancer drug treatment is vitally important in the treatments of patients in all stages of disease. Although the currently available cancer drug treatments improve the survival rate and relieve some symptoms to a certain extent, meanwhile they also produce some unexpected toxic side effects. It is noted that side effects cause patients' health-related quality of life (HRQoL) and patient satisfaction with medication to decrease. Hence, patient-reported outcomes (PROs) (i.e., treatment-related toxicity, the impact of treatments on HRQoL, and patient satisfaction) as an important therapeutic endpoint are increasingly being given a high priority in the management of cancer patients.

In addition, the costs of cancer treatment have increased substantially in the past twenty years. The overall increase in spending for cancer care is due to the increase in both the price and the rates of use, which can be linked to the introduction of new medical technology. Compared with spending in many other areas of heath care, spending on cancer-related medications has risen faster. The strong upward rise causes cancer patients exceptionally affected by high out-of-pocket expenditures, at the same time it gives health economists a great cause for concern. Therefore, economic outcomes, especially understanding the pattern of prescription medication expenditures, are more and more important in cancer outcome research.

However, the literature assessing cancer patients' self-reported outcomes and expenditures, particularly with regards to prescriptions is lacking and mostly out-dated. To meet the demand, this thesis attempted to attribute PROs and expenditures of cancer patients with prescription medications by two empirical cancer outcome researches. One was a macro-level study which examined the factors related

to cancer prescription medication use, HRQoL and prescription medication expenditures in the United States by using national survey data. The other was a meso-level study which examined patient satisfaction and subjective experiences of treatment with breast cancer hormonal medications by using patient self-reported data.

Study One: Impact of Medication on Health-related Quality of Life and Expenditures for Cancer Patients in the United States

The first study used the latest public-used data drawn from the year 2008 Medical Expenditures Panel Survey (MEPS) for research. The MEPS is a nationally representative survey of the civilian non-institutionalized U.S. population conducted by the Agency for Healthcare Research and Quality (AHRQ). In the United States, cancer is the second leading cause of all deaths, which accounts for nearly one of every four deaths.[4] In an attempt to manage cancer, cancer medication plays an important role in the treatment of patients with cancer in all stages of disease. As known from several studies, cancer medication users have impaired HRQoL. In addition, as the largest portion of direct medical expenditures, cancer medication costs greatly increase annually. Nevertheless, there is a dearth of literature which has examined this topic by using nationally representative database such as the MEPS. The primary question for this study's inquiry was "What effects do cancer prescription medications have on the HRQoL and expenditures in patients with cancers?"

Firstly, this study used HRQoL measures to provide different perspectives on health status of cancer patients. The dependent variable - HRQoL, was assessed by using measures of SF-12 for general health status, Kessler Index (K-6) for general psychological distress, and Patient Health Questionnaire (PHQ-2) for depressive symptoms. To my knowledge, this is the first study to examine cancer patients' health status by using of these three different instruments. This study found that medication use for cancer treatment was associated with significant impairment of HRQoL in the U.S. adult cancer population. Specifically, cancer population reported worse physical or mental health, more serious psychological distress and depression than age-matched non-cancer population. These impairments were greater in physical than mental health. It also revealed that differences in the impairment associated with

cancer medication use existed across groups of different characteristics. Patients with less education or chronic diseases had worse HRQoL. In addition, elderly patients indicated poorer physical health, while Hispanics indicated poorer mental health.

Secondly, this study examined how certain demographic or socioeconomic characteristics are strongly associated with high financial burdens. After adjusting for different confounding factors, the adjusted annual mean total and out-of-pocket expenditures associated with cancer prescription medication were $2,572.1 and $597.1, respectively. The multivariate analysis revealed that patient characteristics such as age, region, insurance status, chronic conditions and HRQoL had significant impact on cancer prescription medication expenditures. Total and out-of-pocket expenditures were significantly increased with age. Amidst socioeconomic classes, patients living in the West incurred a lower prescription spending than those living in the other regions. Additionally, patients covered by Medicare insurance paid higher out-of-pocket money for prescription medicine in comparing with those in other insurance groups, and uninsured had the lowest average annual total expense. Patients enrolled under Medicaid or uninsured patients paid less for their medicines by out-of-pocket compared with their counterparts. This deviation gives the researchers and policy makers an alarm of paying attention to those vulnerable people regarding their access to health care. To the best of my knowledge, this study is also the first attempt to assess costs and health status associated with cancer patients taking prescription medications by using a nationally representative database. HRQoL assessment could provide information that is not available from diagnoses or other health record information resources. Meanwhile, it also reveals the patients' thoughts about the efficacy of treatment, which may influence their utilization of medical services. In models to predict medical expenditures, relatively few studies have used self-reported health status as a variable. The present study findings provided the empirical evidences that patients with lower physical SF-12 scores or higher depressive symptoms (PHQ-2) scores are more likely to spend higher out-of-pocket cancer medication expenditures.

Findings from this study give a comprehensive and up-to-date understanding of cancer and cancer prescription expenditures. By examining HRQoL and prescription medication expenditures incurred in cancer patients, especially specific groups of

people, policy makers can assist to determine the best strategy for interventions and perform efficient patient or medical costs management. However, a longitudinal study is needed to determine causal relationships to further test the associations between the medication-related factors and the HRQoL/prescription medication expenditures. Moreover, a more detailed analysis is needed to capture both direct and indirect costs to provide more precise overall predicted prescription medication expenditures for cancer.

Study Two: Patient Satisfaction and Subjective Experiences of Treatment with Breast Cancer Hormonal Medications

The second study examined patient satisfaction and subjective experiences of treatment with breast cancer hormonal medications - tamoxifen and AIs (anastrozole, letrozole, and exemestane). It was conducted based on the patient self-reported data collected from an Internet website www.askapatient.com. This website is designed to provide information about patients' experience with prescription drugs currently approved by the FDA, along with many over-the-counter medicines. It provides high quality information, and it is the best resource for patient opinion about drug performance. This study focused on breast cancer, because breast cancer is the most frequently diagnosed type of cancer among women, and today it is the second leading cause of cancer death in women after lung cancer.[2] Hormonal therapy, including tamoxifen and AIs (anastrozole, letrozole, and exemestane), is the best treatment choice for hormone-receptor-positive breast cancer patients, which make up 75-80% of breast cancer patients.[130, 131] To date, the majority of outcome researches on cancer drug treatment focus on mortality and morbidity, because these outcomes are relatively easy to observe and data are readily available. As know from some publications examining patients' HRQoL, there are no clinically important differences in overall QoL, in spite of the significantly various side effect profiles of tamoxifen and AIs. Hence, the information of patient satisfaction is particularly useful to deeply understand the patients' perspective on their current treatment and differentiate among alternative treatments. Unfortunately, so far there have been no studies assessing patient satisfaction with breast cancer hormonal medications, especially its contributing factors. Therefore, this study is aimed to examine patient satisfaction and subjective experience of treatment with different hormonal medications.

Firstly, this study documented the most common side effects reported by breast cancer patients after taking tamoxifen and AIs. It revealed that patients receiving AIs experienced significantly more arthralgia/myalgia, bone events, carpal tunnel syndrome, vaginal dryness, sexual dysfunction and sleep disorders, while patients receiving tamoxifen experienced significantly more hot flashes, night sweats, vaginal discharge/bleeding and some other serious gynecologic side effects, such as ovarian cysts.

Secondly, this study examined the factors affecting patient satisfaction with hormonal medications. Patient satisfaction is normally studied less frequently than other patient-reported outcomes (e.g., HRQoL). Nevertheless, such PROs are very important in the studies of cancer because they reflect patients' treatment-related behaviours, and consequently, it will impact the quality of life in cancer patients. This information can be served as the baseline for the policy makers on how to best improve cancer outcomes over time and optimize health expenditure. To my knowledge, this is the first study to examine breast cancer patients' satisfaction with different hormonal medications, and examine the contributing factors. This study pointed out that side effects, especially musculoskeletal symptoms and nervous system problems, significantly decreased patient satisfaction. Patients with longer duration of medication treatment, or persisting as current users of medications were more likely to rate a higher score on satisfaction. Compared with tamoxifen patients, anastrozole patients had a significantly higher probability of experiencing satisfaction, and they also had a significantly stronger likelihood of rating a higher score; while letrozole patients only showed a significantly stronger likelihood of rating a higher score.

Findings from this study can help health professionals to focus on more primary breast cancer care from the patient's perspective. A new benchmark for these values can be applied to the management of breast cancer hormonal medications - improve communication between patients and care providers regarding possible side effects, and improve patients' quality of life on hormonal medication therapy. However, it still suggests that further confirmation of the current findings is needed. For example, whether a research in a larger population sample, particularly with longer follow-up

period, or an analysis using the reliable and validated treatment satisfaction questionnaire for medications, report similar results. In addition, researchers should further explore factors impacting on patient satisfaction as well.

Summary

In summary, this thesis employed PROs to conduct empirical research on treatment of cancer patients with prescription medications. It helped establish a framework for comprehensive and up-to-date understanding HRQoL and the real medical expenses spending on cancer-related medications among cancer patients. It was pointed out that cancer medication use was associated with significant impairment of HRQoL. Differences in the impairment also existed across groups of different characteristics. Additionally, total and out-of-pocket prescription medication expenditures were significantly affected by patient characteristics such as age, region, insurance status, chronic conditions and HRQoL. Meanwhile, this study also gave a better understanding of breast cancer patients' subjective experiences and satisfaction with hormonal medications. It revealed that musculoskeletal symptoms or nervous system problems had a significantly negative impact on patient satisfaction, while long-term medication treatment or currently consistent use of medications had a significantly positive impact on patient satisfaction. This thesis provides a new benchmark for these values which can be applied to the management of cancer medications, as well as a reference for future research and baseline into clinical practice. However, further confirmation of the findings from this thesis is needed, and researchers should further explore factors impacting on cancer patients' HRQoL, satisfaction and medication expenditures as well.

Appendices

Appendix 1: ICD-9 Codes for Cancer in Current Study

ICD-9 Codes	Description	Percent (%)
145	Malignant neoplasm of other and unspecified parts of mouth	0.35
149	Malignant neoplasm of other and ill-defined sites within the lip oral cavity and pharynx	0.45
153	Malignant neoplasm of colon	3.16
154	Malignant neoplasm of rectum rectosigmoid junction and anus	0.25
155	Malignant neoplasm of liver and intrahepatic bile ducts	0.75
157	Malignant neoplasm of pancreas	0.40
161	Malignant neoplasm of larynx	0.30
162	Malignant neoplasm of trachea bronchus and lung	3.21
170	Malignant neoplasm of bone and articular cartilage	0.80
171	Malignant neoplasm of connective and other soft tissue	0.30
172	Malignant melanoma of skin	3.31
173	Other malignant neoplasm of skin	17.24
174	Malignant neoplasm of female breast	8.62
179	Malignant neoplasm of uterus-part unspecified	2.06
180	Malignant neoplasm of cervix uteri	1.70
185	Malignant neoplasm of prostate	7.62
186	Malignant neoplasm of testis	0.50
188	Malignant neoplasm of bladder	1.40
189	Malignant neoplasm of kidney and other and unspecified urinary organs	1.30
193	Malignant neoplasm of thyroid gland	1.60
195	Malignant neoplasm of other and ill-defined sites	0.30
198	Secondary malignant neoplasm of other specified sites	1.15
199	Malignant neoplasm without specification of site	2.71
202	Other malignant neoplasms of lymphoid and histiocytic tissue	2.36
207	Other specified leukemia	0.35
208	Leukemia of unspecified cell type	1.50
211	Benign neoplasm of other parts of digestive system	2.81
214	Lipoma	0.90
215	Other benign neoplasm of connective and other soft tissue	2.91
216	Benign neoplasm of skin	9.17
217	Benign neoplasm of breast	0.40
218	Uterine leiomyoma	1.30
228	Hemangioma and lymphangioma any site	0.25
229	Benign neoplasm of other and unspecified sites	2.46
232	Carcinoma in situ of skin	2.81
237	Neoplasm of uncertain behavior of endocrine glands and nervous system	0.30
238	Neoplasm of uncertain behavior of other and unspecified sites and tissues	0.95
239	Neoplasms of unspecified nature	12.03

Appendix 2: The U.S. states for Each Region

Region	States
Northeast	Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont
Midwest	Indiana, Illinois, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin
South	Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia
West	Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming

Agency for Healthcare Research and Quality, MEPS HC-121: 2008 Full Year Consolidated Data File.[104]

Appendix 3: Self-Administered Questionnaire (SAQ) 2008

2008

Your Health and Health Opinions

Your opinion matters!

MEPS
Medical Expenditure Panel Survey

Understanding how people feel about their health and health care is an important goal of MEPS. Please take a few minutes to answer the questions in this booklet.

Survey Instructions

- Please answer every question by checking one box "✓." If you are unsure about how to answer a question, please give the best answer you can.
- You are sometimes told to skip over some questions in this survey. When this happens you will see arrows that tell you what questions to answer next, like this:

1 ☐ Yes
2 ☐ No → **Skip to Question 3**

Next Question

This Booklet Should Be Completed By →

RUID: PID:

Name:

Version: DOB: Panel/ Round:

Attach label here (see back cover) →

Your participation is voluntary and all of your answers will be kept confidential. If you have any questions about this booklet, please call Alex Scott at 1-800-945-MEPS (6377).

When you have completed the booklet, please seal it with this label → and place it in the envelope provided. Have it ready to give to your interviewer at his or her next visit.

The Agency for Healthcare Research and Quality and
The Centers for Disease Control and Prevention of the
U.S. Department of Health and Human Services

START HERE

Your Health Care in the Last 12 Months

1. In the last 12 months, did you have an illness, injury, or condition that needed care right away in a clinic, emergency room, or doctor's office?

1 ☐ Yes
2 ☐ No → **Skip to Question 3**

2. In the last 12 months, when you needed care right away how often did you get care as soon as you thought you needed?

1 ☐ Never
2 ☐ Sometimes
3 ☐ Usually
4 ☐ Always

3. In the last 12 months, not counting the times you needed care right away, did you make any appointments for your health care at a doctor's office or clinic?

1 ☐ Yes
2 ☐ No → **Skip to Question 5**

4. In the last 12 months, not counting the times you needed care right away, how often did you get an appointment for your health care at a doctor's office or clinic as soon as you thought you needed?

1 ☐ Never
2 ☐ Sometimes
3 ☐ Usually
4 ☐ Always

5. In the last 12 months, not counting the times you went to an emergency room, how many times did you go to a doctor's office or clinic to get health care for yourself?

0 ☐ None → **Skip to Question 13**
1 ☐ 1
2 ☐ 2
3 ☐ 3
4 ☐ 4
5 ☐ 5 to 9
6 ☐ 10 or more

6. In the last 12 months, did you or a doctor believe you needed any care, tests, or treatment?

1 ☐ Yes
2 ☐ No → **Skip to Question 8**

7. In the last 12 months, how often was it easy to get the care, tests, or treatment you or a doctor believed necessary?

1 ☐ Never
2 ☐ Sometimes
3 ☐ Usually
4 ☐ Always

8. In the last 12 months, how often did doctors or other health providers listen carefully to you?

1 ☐ Never
2 ☐ Sometimes
3 ☐ Usually
4 ☐ Always

9. In the last 12 months, how often did doctors or other health providers explain things in a way that was easy to understand?

1 ☐ Never
2 ☐ Sometimes
3 ☐ Usually
4 ☐ Always

Please go to page 3 →

10. In the last 12 months, how often did doctors or other health providers show respect for what you had to say?

1 ☐ Never
2 ☐ Sometimes
3 ☐ Usually
4 ☐ Always

11. In the last 12 months, how often did doctors or other health providers spend enough time with you?

1 ☐ Never
2 ☐ Sometimes
3 ☐ Usually
4 ☐ Always

12. Using any number from 0 to 10 where 0 is the worst health care possible and 10 is the best health care possible, what number would you use to rate all your health care in the last 12 months?

☐ 0 Worst health care possible
☐ 1
☐ 2
☐ 3
☐ 4
☐ 5
☐ 6
☐ 7
☐ 8
☐ 9
☐ 10 Best health care possible

13. Do you currently smoke?

1 ☐ Yes
2 ☐ No → **Skip to Question 15**

14. In the last 12 months did a doctor advise you to quit smoking?

1 ☐ Yes
2 ☐ No
3 ☐ Had no visits in the last 12 months

15. In the last 2 years, has your blood pressure been checked by a doctor, nurse, or other health professional?

1 ☐ Yes
2 ☐ No

Getting Health Care from a Specialist

When you answer the next questions, do not include dental visits.

16. Specialists are doctors like surgeons, heart doctors, allergy doctors, skin doctors, and others who specialize in one area of health care.

In the last 12 months, did you or a doctor think you needed to see a specialist?

1 ☐ Yes
2 ☐ No → **Skip to Question 18**

17. In the last 12 months, how often was it easy to see a specialist that you needed to see?

1 ☐ Never
2 ☐ Sometimes
3 ☐ Usually
4 ☐ Always

Please go to page 4 →

General Health

18. In general, would you say your health is:

1 ☐ Excellent
2 ☐ Very good
3 ☐ Good
4 ☐ Fair
5 ☐ Poor

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

19. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

1 ☐ Yes, limited a lot
2 ☐ Yes, limited a little
3 ☐ No, not limited at all

20. Climbing several flights of stairs

1 ☐ Yes, limited a lot
2 ☐ Yes, limited a little
3 ☐ No, not limited at all

During the past 4 weeks how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

21. Accomplished less than you would like

1 ☐ All of the time
2 ☐ Most of the time
3 ☐ Some of the time
4 ☐ A little of the time
5 ☐ None of the time

22. Were limited in the kind of work or other activities

1 ☐ All of the time
2 ☐ Most of the time
3 ☐ Some of the time
4 ☐ A little of the time
5 ☐ None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

23. Accomplished less than you would like

1 ☐ All of the time
2 ☐ Most of the time
3 ☐ Some of the time
4 ☐ A little of the time
5 ☐ None of the time

24. Did work or other activities less carefully than usual

1 ☐ All of the time
2 ☐ Most of the time
3 ☐ Some of the time
4 ☐ A little of the time
5 ☐ None of the time

Please go to page 5 →

25. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

1 ☐ Not at all
2 ☐ A little bit
3 ☐ Moderately
4 ☐ Quite a bit
5 ☐ Extremely

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks:

26. Have you felt calm and peaceful?

1 ☐ All of the time
2 ☐ Most of the time
3 ☐ Some of the time
4 ☐ A little of the time
5 ☐ None of the time

27. Did you have a lot of energy?

1 ☐ All of the time
2 ☐ Most of the time
3 ☐ Some of the time
4 ☐ A little of the time
5 ☐ None of the time

28. Have you felt downhearted and depressed?

1 ☐ All of the time
2 ☐ Most of the time
3 ☐ Some of the time
4 ☐ A little of the time
5 ☐ None of the time

29. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

1 ☐ All of the time
2 ☐ Most of the time
3 ☐ Some of the time
4 ☐ A little of the time
5 ☐ None of the time

Please go to page 6 →

The following questions ask about how you have been feeling during the past 30 days. For each question, please place a check mark in the box that best describes how often you had this feeling.

During the past 30 days, about how often did you feel...	All of the time	Most of the time	Some of the time	A little of the time	None of the time
30. ...nervous?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
31. ...hopeless?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
32. ...restless or fidgety?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
33. ...so sad that nothing could cheer you up?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
34. ...that everything was an effort?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
35. ...worthless?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

The following two questions ask about how you have been feeling in the past 2 weeks.

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Nearly every day	More than half the days	Several days	Not at all
36. Little interest or pleasure in doing things.	1 ☐	2 ☐	3 ☐	4 ☐
37. Feeling down, depressed, or hopeless.	1 ☐	2 ☐	3 ☐	4 ☐

Please go to page 7

Opinions about Health

For items 38-41, please check one of the boxes to indicate how strongly you agree or disagree for each statement. If you are uncertain, check the box for uncertain (3 ☐).

	Disagree strongly	Disagree somewhat	Uncertain	Agree somewhat	Agree strongly
38. I'm healthy enough that I really don't need health insurance.	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
39. Health insurance is not worth the money it costs.	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
40. I'm more likely to take risks than the average person.	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
41. I can overcome illness without help from a medically trained person.	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

Date completed: _____

If this booklet was not completed by the person named on the front, who completed it: _____

What is this person's relationship to the person named on the front: _____

Thank you for taking the time to complete this survey.

Remember to seal it and place it in the envelope provided.

Cited from MEPS website [42]

Abbreviation

ACS: American Cancer Society

AHRQ: Agency for Healthcare Research and Quality

AI: Aromatase Inhibitor

ALIQUOT: Anastrozole vs. Letrozole, an Investigation of Quality Of Life and Tolerability

ATAC: Arimidex, Tamoxifen Alone or in Combination

BCQ: Breast Chemotherapy Questionnaire

BIG: Breast International Group

CASC: Comprehensive Assessment of Satisfaction with Care

CDC: Centers for Disease Control and Prevention

CES-D: Centre for Epidemiological Studies-Depression Scale

CHAMPVA: Civilian Health and Medical Program of the Department of Veterans Affairs

CMS: Centers for Medicare & Medicaid Services

C-PET: Checklist for Patients with Endocrine Therapy

CTSQ: Cancer Therapy Satisfaction Questionnaire

EORTC QLQ C-30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30

EPIC: Expanded Prostate Cancer Index Composite

EWB: Emotional Well-Being

FACIT: Functional Assessment of Chronic Illness Therapy

FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer

FACT-ES: Functional Assessment of Cancer Therapy-Endocrine Subscale

FACT-G: Functional Assessment of Cancer Therapy-General

FDA: Food and Drug Administration

FLIC: Functional Living Index Cancer

FWB: Functional Well-Being

GDP: Gross Domestic Product

HAQ: Health Assessment Questionnaire

HC: Household Component

HCUP: Healthcare Cost and Utilization Project

HHS: Health and Human Services

HMOS: Health Maintenance Organizations

NCI: National Cancer Institute

NHP: Nottingham Health Profile

NIH: National Institutes of Health

HRQoL: Health-related Quality of Life

HUI: Health Utilities Index

IARC: International Agency for Research on Cancer

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

IES: Intergroup Exemestane Study

IRR: Incidence Rate Ratio

KPS: Karnofsky Performance Status

K-6: Kessler Index

LSQ: Life Satisfaction Questionnaire

MCID: Minimal Clinically Important Difference

MCS: Mental Component Summary

MENQOL: Menopause-specific Quality of Life Questionnaire

MEPS: Medical Expenditure Panel Survey

MOS: Medical Outcomes Study

MRS: Mood Rating Scale

MSA: Metropolitan Statistical Area

NAMCS: National Ambulatory Medical Care Survey

NCI: National Cancer Institute

NDC: National Drug Code

NHIS: National Health Interview Survey

NIH: National Institutes of Health

NSABP: National Surgical Adjuvant Breast and Bowel Project

NSAS BC: National Surgical Adjuvant in Study of Breast Cancer

OECD: Organization for Economic Cooperation and Development

OLS: Ordinary Least Squares

OR: Odds Ratio

PCI: Prostate Cancer Index

PCS: Physical Component Summary

PHQ-2: Patient Health Questionnaire

POMS: Profile of Mood States

PROs: Patient Reported Outcomes

PSUS: Primary Sampling Units

PWB: Physical Well-Being

QALY: Quality-Adjusted Life Year

QoL: Quality of Life

QOLI: Quality of Life Inventory

Q-TWiST: Quality-adjusted Time Without Symptoms or Toxicity

QWB: Quality of Well-Being

RSCL: Rotterdam Symptom Checklist

SAQ: Self-Administered Questionnaire

SATMED-Q: Treatment Satisfaction with Medications Questionnaire

SES: Socioeconomic Status

SF-36: Medical Outcomes Study 36-item Short Form Health Survey

SF-12v2: Medical Outcomes Study 12-item Short Form Health Survey, Version 2

SG: Standard Gamble

SWB: Social Well-Being

TEAM: Tamoxifen Exemestane Adjuvant Multinational

TRICARE: Military Health Services

TSQM: Treatment Satisfaction Questionnaire for Medication

TOI: Trial Outcome Index

TRA: Theory of Reasoned Action

TTO: Time Trade-Off

VA: Veterans Administration

VAMS: Visual Analogical Mental Scales

VAS: Visual Analogue Scales

WHO: World Health Organization

References

1 What is cancer? National Cancer Institute, U.S. National Institutes of Health. Available at: http://www.cancer.gov/cancertopics/what-is-cancer. Accessed May 24, 2010.

2 World Cancer Report 2008, World Health Organization, International Agency for Research on Cancer. Available at: http://www.iarc.fr/en/publications/pdfs-online/wcr/2008/index.php. Accessed May 24, 2010.

3 OECD Health Data 2010: Statistics and Indicators. Available at: http://www.oecd.org/document/30/0,3343,en_2649_34631_12968734_1_1_1_1,00.html. Accessed Aug 10, 2010.

4 Cancer Facts and Figures. American Cancer Society. Available at: http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/index.Accessed Aug 10, 2010.

5 Cancer Trends Progress Report - 2009/2010 Update, National Cancer Institute. Available at: http://progressreport.cancer.gov. Accessed Aug 10, 2010.

6 Tangka FK, Trogdon JG, Richardson LC, et al. Cancer treatment cost in the United States: has the burden shifted over time? Cancer, 2010 Jul 15; 116 (14):3477-84.

7 Bach PB. Limits on Medicare's Ability to Control Rising Spending on Cancer Drugs. N Engl J Med 2009; 360:626-633.

8 USA Today Examines Insurers', Patients' Concern Over Increased Cost of Cancer Drugs [Jul 11, 2006]. Available at: http://www.medicalnewstoday.com/articles/47063.php. Accessed Feb 2, 2011.

9 Montz E, Seshamani M. Fighting Back Against Cancer: Health Insurance Reform & Cancer in America. Available at: http://www.healthreform.gov/reports/fightingcancer/index.html. Accessed Aug 10, 2010.

10 Lipscomb J, Donaldson MS, Hiatt RA. Cancer outcomes research and the arenas of application. J Natl Cancer Inst Monogr 2004; 33:1–7.

11 Neumann PJ, Goldie SJ, Weinstein MC. Preference-Based Measures in Economic Evaluation in Health Care. Annu. Rev. Public Health 2000. 21:587–611.

12 National Cancer Institute: The Nation's investment in cancer research: A plan and budget proposal for fiscal year 2008. National Institutes of Health Publication No. 06-6090. Available at: http://plan.cancer.gov/plan_overview.shtml. Accessed Jan 14, 2009.

13 2015 Goals of the American Cancer Society. American Cancer Society. Available at: http://www.cancer.org/docroot/COM/content/div_PA/COM_4_2X_Volunteer_11087.asp. Accessed Jan 14, 2009.

14 Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Health Qual Life Outcomes 2006; 4: 79.

15 Sloan JA, Halyard MY, Frost MH et al. The Mayo Clinic Manuscript Series Relative to the Discussion, Dissemination, and Operationalization of the Food and Drug Administration Guidance on Patient-Reported Outcomes. Value Health, 2007 Nov-Dec; 10 Suppl 2:S59-63.

16 WHO-QOL. World Health Organization Quality of Life-100. Geneva: World Health Organization, Division of Mental Health; 1995. Report No.: 100.

17 Brown ML, Lipscomb J, Snyder C. The Burden of Illness of Cancer: Economic Cost and Quality of Life. Annu. Rev. Public Health 2001: 22:91–113.

18 Liu J, Mittendorf T, von der Schulenburg JM. A structured review and guide through studies on health-related quality of life in kidney cancer, hepatocellular carcinoma, and leukemia. Cancer Invest. 2010 Mar; 28(3):312-22.

19 Patsi Sinnott. Introduction to Effectiveness, Patient Preferences and Utilities. HERC Economics Course. May 6, 2009. Available at: www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/hcea-050609.ppt. Accessed Aug 10, 2010.

20 Riepe MW, Mittendorf T, Förstl H et al. Quality of Life as an outcome in Alzheimer's disease and other dementias- obstacles and goals. BMC Neurol 2009 Aug 25; 9:47.

21 Tolley KH. What are health utilities? What is series, 2009. Hayward Medical Communications' evidence-based medicine (EBM) web pages. Available at: www.whatisseries.co.uk. Accessed Aug 10, 2010.

22 Brazier J, Deverill M et al. A review of the use of health status measures in economic evaluation. Health Technology Assessment 1999; 3(9):8.

23 Phillips C, Thompson G. What is a QALY? What is series, 2009. Hayward Medical Communications' evidence-based medicine (EBM) web pages. Available at: http://www.medicine.ox.ac.uk. Accessed Aug 10, 2010.

24 Lubeck DP. Patient-Reported Outcomes and Their Role in the Assessment of Rheumatoid Arthritis. Pharmacoeconomics. 2004; 22(2 Suppl 1):27-38.

25 Geitona M, Kyriopoulos J, Zavras J, Theodoratou T, Alexopoulos EC. Medication use and patient satisfaction: a population based survey. Fam Pract 2008; 25: 362–369.

26 Shikiar R, Rentz AM. Satisfaction with Medication: An Overview of Conceptual,Methodologic, and Regulatory Issues. Value Health 2004 Mar-Apr; 7(2):204-15.

27 Clauser SB. Use of Cancer Performance Measures in Population Health: A Macro-level Perspective. J Natl Cancer Inst Monogr 2004; 33:142–54.

28 Bredart A, Razavi D, Delvaux N et al. A comprehensive assessment of satisfaction with care for cancer patients. Support Care Cancer 1998, 6:518–523.

29 Bredart A, Razavi D, Robertson C et al. A comprehensive assessment of satisfaction with care: preliminary psychometric analysis in French, Polish, Swedish and Italian oncology patients. Patient Educ Couns. 2001 Jun; 43(3):243-52.

30 Atkinson MJ, Sinha A, Hass SL et al. Validation of a general measure of treatment satisfaction - the Treatment Satisfaction Questionnaire for Medication (TSQM) - using a national panel study of chronic disease. Health Qual Life Outcomes 2004; 2:12.

31 Atkinson MJ, Kumar R, Cappelleri JC, Hass SL. Hierarchical construct validity of the "Treatment Satisfaction Questionnaire for Medication" (TSQM Version II) among outpatient pharmacy consumers. Value Health 2005; 8(Suppl. 1):S9–24.

32 Ruiz MA, Pardo A, Rejas J et al. Development and validation of the "Treatment Satisfaction with Medicines Questionnaire" (SATMED-Q). Value Health 2008: 11, 913-926.

33 Abetz L, Coombs JH, Keininger DL et al. Development of the cancer therapy satisfaction questionnaire: Item generation and content validity testing. Value in Health 2005; 8, S41-S53.

34 Trask PC, Tellefsen C, Espindle D et al. Psychometric Validation of the Cancer Therapy Satisfaction Questionnaire. Value Health 2008 Jul-Aug; 11(4):669-79.

35 Asadi-Lari M, Packham C, Gray D. Patients' satisfaction and quality of life in coronary artery disease. Health Qual Life Outcomes. 2003 Oct 22; 1:57.

36 Fryback DG, Craig BM. Measuring Economic Outcomes of Cancer. J Natl Cancer Inst Monogr 2004; (33):134-41.

37 Luce BR, Manning WG, Siegel JE, Lipscomb J. Estimating Costs in Cost-Effectiveness Analysis. In: Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-Effectiveness in Health and Medicine. New York: Oxford University Press, 1996, P179.

38 Yabroff KR, Lawrence WF, Clauser S et al. Burden of Illness in Cancer Survivors: Findings From a Population-Based National Sample. J Natl Cancer Inst 2004; 96:1322–30.

39 Neumann PJ, Goldie SJ, Weinstein MC. Rereference-Based Measures in Economic Evaluation in Health Care. Annu Rev Public Health 2000; 21:587-611.

40 McFarlane PA, Bayoumi AM. Acceptance and rejection: cost-effectiveness and the working nephrologist. Kidney Int 2004 Nov; 66(5):1735-41.

41 Lipscomb J, Donaldson MS, Arora NK et al. Cancer Outcomes Research. J Natl Cancer Inst Monogr. 2004; (33):178-97.

42 Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality. Available at: http://www.meps.ahrq.gov/mepsweb/. Accessed Oct 01, 2011.

43 Lipscomb J, Gotay CC, Snyder CF. Patient-reported Outcomes in Cancer: A Review of Recent Research and Policy Initiatives. CA Cancer J Clin 2007 Sep-Oct; 57(5):278-300.

44 Baker F, Haffer SC, Denniston M. Health-Related Quality of Life of Cancer and Noncancer Patients in Medicare Managed Care. Cancer 2003; 97:674–81.

45 Holzner B, Kemmler G, Kopp M et al. Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. Eur J Haematol. 2004. Jun; 72 (6): 381-389.

46 Kondo Y, Yoshida H, Tateishi R et al. Health-related quality of life of chronic liver disease patients with and without hepatocellular carcinoma. J Gastroenterol Hepatol 2007; 22:197–203.

47 Steel JL, Chopra K, Olek MC et al. Health-related quality of life: hepatocellular carcinoma, chronic liver disease, and the general population. Qual Life Res 2007; 16:203–215.

48 Botella-Carretero JI., Galan JM., Caballero C et al. Quality of life and psychometric functionality in patients with differentiated thyroid carcinoma. Endocrine-Related Cancer, 2003; 10, 601–610.

49 Pelttari H, Sintonen H, Schalin-Jäntti C, Välimäki MJ. Health-related quality of life in long-term follow-up of patients with cured TNM Stage I or II differentiated thyroid carcinoma. Clin Endocrinol (Oxf). 2009 Mar; 70(3):493-7. Epub 2008 Aug 4.

50 Alibhai SM, Breunis H, Timilshina N et al. Impact of Androgen Deprivation Therapy on Physical Function and Quality of Life in Men With Non-Metastatic Prostate Cancer. J Clin Oncol 2010, 28: 5030-7.

51 Kobayashi K, Shimonagayoshi M, Kobayashi M et al. Relationship among socioeconomic factors, distress, and quality of life (QOL) in cancer outpatients. 2004 ASCO Annual Meeting Abstract: 8127.

52 Penson D, Litwin M, Lubeck D, Flanders S, Pasta D, Carroll P. Transitions in health-related quality of life during the first nine months after diagnosis with prostate cancer. Prostate Cancer Prostatic Dis 1998; 1:134–43.

53 Penson DF, Stoddard ML, Pasta DJ et al. The association between socioeconomic status, health insurance coverage, and quality of life in men with prostate cancer. J Clin Epidemiol 2001; 54(4):350–8.

54 Krupski TL, Fink A, Kwan L et al. Health-related quality-of-life in low-income, uninsured men with prostate cancer.J Health Care Poor Underserved 2005 May; 16(2):375-90.

55 Knight SJ, Latini DM, Hart SL et al. Education predicts quality of life among men with prostate cancer cared for in the department of veterans affairs - A longitudinal quality of life analysis from CaPSURE. Cancer 2007; 109, 1769-1776.

56 Melmed GY, Kwan L, Reid K et al. Quality of life at the end of life: trends in patients with metastatic prostate cancer. Urology 2002; 59(1):103–9.

57 Janz NK, Mujahid MS, Lantz PM et al. Population-based study of the relationship of treatment and sociodemographics on quality of life for early stage breast cancer. Qual Life Res 2005; 14:1467–79.

58 Friedman LC, Kalidas M, Elledge R et al. Optimism, social support and psychosocial functioning among women with breast cancer. Psycho-oncology 2006; 15 (7):595–603.

59 Costanzo ES, Lutgendorf SK, Mattes ML et al. Adjusting to life after treatment: distress and quality of life following treatment for breast cancer. Br J Cancer 2007; 97(12):1625–31.

60 Ashing-Giwa K, Tejero JS, Kim J, Padilla GV, Hellemann G. Examining predictive models of HRQOL in a population-based, multiethnic sample of women with breast carcinoma. Qual Life Res 2007; 16:413–28.

61 Kornblith AB, Powell M, Regan MM et al. Long-term psychosocial adjustment of older vs. younger survivors of breast and endometrial cancer. Psycho-oncology 2007; 16:895–903.

62 Janz NK, Mujahid MS, Hawley ST et al. Racial/ethnic differences in adequacy of information and support for women with breast cancer. Cancer 2008; 113: 1058–67.

63 Chae YR, Seo K. Health-Related Quality of Life in Women With Breast Cancer in Korea: Do Sociodemographic Characteristics and Time Since Diagnosis Make a Difference? Oncol Nurs Forum. 2010 Jul; 37(4):E295-303.

64 Fatone AM, Moadel AB, Foley FW, Fleming M, Jandorf L. Urban voices: the quality-of-life experience among women of color with breast cancer. Palliat Support Care 2007; 5:115–25.

65 Culver JL, Arena PL, Antoni MH et al. Coping and distress among women under treatment for early stage breast cancer: Comparing African Americans, Hispanics, and non-Hispanic Whites. Psychooncology 2002; 11:495–504.

66 Rao D, Debb S, Blitz D et al. Racial/Ethnic Differences in the Health- Related Quality of Life of Cancer Patients. J Pain Symptom Manage 2008; 36:488-496.

67 Janz NK, Mujahid MS, Hawley ST et al. Racial/ethnic differences in quality of life after diagnosis of breast cancer. J Cancer Surviv 2009; 3:212–222.

68 Montazeri A, Hole D, Milroy R et al. Quality of life in lung cancer patients: does socioeconomic status matter? Health Qual Life Outcomes 2003; 1: 19.

69 van Loon AJ, Goldbohm RA, van den Brandt PA. Lung cancer: is there an association with socioeconomic status in the Netherlands? J Epidemiol Community Health 1995 Feb; 49 (1):65-69.

70 McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993 Mar; 31(3):247-63.

71 Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30 (6):473–83.

72 Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 Health survey manual and interpretation guide Boston, MA: The Health Institute, New England Medical Center; 1993.

73 Khosla A. Prescription asthma medication expenditures: are there social disparities? Available at: http://esr.lib.ttu.edu/handle/2346/21024?show=full. Accessed April 5, 2011.

74 Lines LM. Out-of-pocket expenditures by cancer patients in the United States: A Population-Based Analysis. Available at: http:// lisalines.com. Accessed April 5, 2011.

75 Diehr P, Yanez D, Ash A et al. Methods for analyzing health care utilization and costs. Annu. Rev. Public Health. 1999. 20:125–44.

76 Cohen JW, Machlin SR, Zuvekas SH et al. Health care expenses in the United States, 1996. Rockville (MD): Agency for Healthcare Research and Quality; 2000. MEPS Research Findings No. 12. AHRQ Pub. No. 01-0009.

77 Ezzati-Rice TM, Kashihara D, Machlin SR. Health care expenses in the United States, 2000. Rockville (MD): Agency for Healthcare Research and Quality; 2004. MEPS Research Findings No. 21. AHRQ Pub. No. 04-0022.

78 Xu KT. Financial disparities in prescription drug use between elderly and nonelderly Americans. Health Aff (Millwood). Sep-Oct 2003; 22 (5):210-221.

79 McKercher PL, Taylor SD, Lee JA, Chao J, Kumar RN. Prescription drug use among elderly and nonelderly families. J Manag Care Pharm. Jan-Feb 2003; 9 (1):19-28.

80 Hodgson TA, Cohen AJ. Medical Expenditures for Major Diseases, 1995. Health Care Financ Rev. 1999 Winter; 21(2):119-64.

81 Medicare Chartbook, Fourth edition, 2010. Available at: www.collaborationhealthcare.com/11-9-10KFFMedicareChartBook2010.pdf. Accessed at Mar 15th.2011.

82 Cancer Facts & Figures for African Americans 2009-2010. American Cancer Society. Available at: http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFiguresforAfricanAmericans/cancer-facts-figures-for-african-americans-2009-2010. Accessed Mar 15, 2011.

83 Cancer Facts & Figures for Hispanics/ Latinos 2009-2011. American Cancer Society. Available at: http://www.cancer.org/research/cancerfactsfigures/cancerfactsfiguresforhispanicslatinos/cancer-facts--figures-for-hispanics-latinos-2009-2011. Accessed Mar 15, 2011.

84 Hargraves JL. Trends in health insurance coverage and access among black, Latino and white Americans, 2001-2003. Tracking Report. (11):1-6, 2004 Oct.

85 Dunlop DD, Manheim LM, Song J, Chang RW. Gender and ethnic/racial disparities in health care utilization among older adults. J Gerontol B Psychol Sci Soc Sci. Jul 2002; 57(4):S221-233.

86 Winters KP, Wyatt SB, Nick TG et al. Race, stability of health insurance coverage, and prescription medication use. ABNF Journal 2010; 21(1); 21-26.

87 Tseng CW, Tierney EF, Gerzoff RB et al. Race/Ethnicity and Economic Differences in Cost-Related Medication Underuse Among Insured Adults With Diabetes. Diabetes Care 2008; 31:261–266.

88 Shin J, Moon S. Prescription Drug Insurance: Effects on Drug Use, Expenditure and Out-of-Pocket Spending Among the Near-Elderly. Abstr AcademyHealth Meet 2005; 22: abstract no. 3477.

89 Stagnitti MN. Outpatient Prescribed Medicine Expenses by Source of Payment and Insurance Status for the Medicare and Non-Medicare Populations, 2003. Statistical Brief 125. May 2006. Agency for Healthcare Research and Quality, Rockville, Md.

90 Heisler M, Langa KM, Eby EL et al. The health effects of restricting prescription medication use because of cost. Med Care 2004; 42: 626–634.

91 Harman JS, Kelleher KJ, Reynolds CF, Pincus HA. Out-of-pocket healthcare expenditures of older Americans with depression. J Am Geriatr Soc. 2004 May; 52(5):809-13.

92 Farmer, M. and K. Ferraro. Are Racial Disparities in Health Conditional on Socioeconomic Status? Social Science and Medicine 2005; 60: 191-204.

93 Lee CS, Skrepnek GH. Physical Activity Makes a Difference: Out-of-Pocket Health Care Expenditure and Quality-of-Life in Patients with Primary Hypertension. Circulation 2010; 122:A19891.

94 You X, Kobayashi Y. Determinants of Out-of-Pocket Health Expenditure in China: Analysis Using China Health and Nutrition Survey Data. Appl Health Econ Health Policy 2011; 9(1):39-49.

95 Howard DH, Molinari NA, Thorpe KE. National estimates of medical costs incurred by nonelderly cancer patients. Cancer, 2004; 100 (5), 883-891.

96 Thorpe KE, Howard D. Health insurance and spending among cancer patients. Health Aff (Millwood), Suppl Web Exclusives, 2003; W3-189-198.

97 Banthin JS, Bernard DM. Changes in financial burdens for health care: national estimates for the population younger than 65 years, 1996 to 2003. JAMA, 2006; 296(22), 2712-2719.

98 Langa KM, Fendrick AM, Chernew ME et al. Out-of-Pocket Health-Care Expenditures among Older Americans with Cancer. Value in Health, 2004; 7(2), 186-194.

99 Short PF, Moran JR, Punekar R. Medical Expenditures of Adult Cancer Survivors Aged < 65 Years in the United States. Cancer 2011; 117 (12):2791-800.

100 Arozullah AM, Calhoun EA, Wolf M et al. The financial burden of cancer: estimates from a study of insured women with breast cancer. J Support Oncol, 2004; 2(3), 271-278.

101 Xie J, Wu EQ, Zheng ZJ et al. Patient-reported health status in coronary heart disease in the United States: age, sex, racial, and ethnic differences. Circulation. 2008 Jul 29; 118(5):491-7.

102 LN Sung. The effect of selected comorbid diseases on the total outpatient payments in patients with diabetes mellitus. Available at: http://gradworks.umi.com/31/81/3181994.html. Accessed April 5, 2011.

103 Wu AW, Snyder C, Clancy CM, Steinwachs DM. Adding the Patient Perspective to Comparative Effectiveness Research. Health Affairs (Millwood), 2010 Oct; 29(10):1863-71.

104 MEPS HC-121: 2008 Full Year Consolidated Data File. November 2010. Agency for Healthcare Research and Quality. Available at: http://www.meps.ahrq.gov/mepsweb/data_stats/download_data_files_detail.jsp?cboPufNumber=HC-121

105 Cohen SB. The Medical Expenditure Panel Survey: An Overview. Eff Clin Pract. 2002 May-Jun; 5(3 Suppl):E1.

106 MEPS HC-118A: 2008 Prescribed Medicines. October 2010. Agency for Healthcare Research and Quality. Available at: http://www.meps.ahrq.gov/mepsweb/data_stats/download_data_files_detail.jsp?cboPufNumber=HC-118A

107 MEPS HC-120: 2008 Medical Conditions. November 2010. Agency for Healthcare Research and Quality. Available at: http://www.meps.ahrq.gov/mepsweb/data_stats/download_data_files_detail.jsp?cboPufNumber=HC-120

108 Egede LE, Zheng D, Simpson K. Comorbid Depression is Associated With Increased Health Care Use and Expenditures in Individuals With Diabetes. Diabetes Care. 2002 Mar; 25(3):464-70.

109 Krauss N, Kass B. Comparison of household and medical provider reports of medical conditions. August 2000. Paper presented August 15 at the Joint Statistical Meetings, Indianapolis, Indiana.

110 Thorpe KE, Florence CS, Joski P. Which Medical Conditions Account For the Rise in Health Care Spending? Health Affairs-The Policy Journal of the Health Sphere, 2004; 25 August.

111 Moeller JF, Stagnitti MN, Horan E et al. Outpatient Prescription Drugs: Data Collection and Editing in the 1996 Medical Expenditure Panel Survey (HC-010A) (MEPS Methodology Report No. 12). Rockville, MD: Agency for Healthcare Research and Quality; 2001; 1-20.

112 Jenkinson C, Layte R, Jenkinson D et al. A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? J Public Health Med 1997; 19:179–86.

113 Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996; 34:220 –233.

114 Ware JE, Jr. SF-12v2TM How to score version 2 of the SF-12 Health Survey. Boston: Quality Metric Incorporated 1995.

115 Cheak-Zamora NC, Wyrwich KW, McBride TD. Reliability and validity of the SF-12v2 in the medical expenditure panel survey. Qual Life Res 2009; 18:727–735.

116 Kessler RC, Andrews G, Colpe LJ et al. Short screening scales to monitor population prevalence and trends in non-specific psychological distress. Psychological Medicine 2002; 32: 959-976.

117 Kessler RC, Barker PR, Colpe LJ et al. Screening for serious mental illness in the general population Archives of General Psychiatry. 2003; 60(2), 184-189.

118 Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: Validity of a two-item depressive screener. Medical Care 2003; 41: 1284-1292.

119 Hwang W, Weller W, Ireys H, Anderson G.Out-Of-Pocket Medical Spending For Care Of Chronic Conditions. Health Aff (Millwood). 2001 Nov-Dec; 20(6):267-78.

120 Ibrahim SA, Burant CH, Siminoff LA et al. Self-assessed global quality of life: A comparison between African-American and white older patients with arthritis. Journal of Clinical Epidemiology 2002; 55; 512-517.

121 The SURVEYREG Procedure. SAS/STAT® User's Guide, Version 8, Cary, NC: SAS Institute Inc., 1999.

122 Balu S, Thomas J 3rd. Incremental expenditure of treating hypertension in the United States. Am J Hyperten. 2006 Aug; 19(8):810-6; discussion 817.

123 Hays RD, Morales LS. The RAND-36 measure of health related quality of life. Ann Med. 2001; 33:350 -7.

124 Wang HM, Beyer M, Gensichen J, Gerlach FM. Health-related quality of life among general practice patients with differing chronic diseases in Germany: cross sectional survey. BMC Public Health 2008, 8:246.

125 Cohen J. Statistical power analysis for the behavioral sciences (2nd ed.).1988.

126 Fleishman JA, Cohen JW, Manning WG, Kosinsik M. Using the SF-12 health status measure to improve predictions of medical expenditures. Med Care. 2006 May; 44(5 Suppl):I54-63.

127 What is breast cancer? Breastcancer.org. Available at: http://www.breastcancer.org/symptoms/understand_bc/what_is_bc.jsp. Accessed May 24, 2010

128 Breast Cancer Facts & Figures 2009-2010. American Cancer society. Available at: http://www.cancer.org/Research/CancerFactsFigures/BreastCancerFactsFigures/index. Accessed May 24, 2010.

129 Medications Effective in Reducing Risk of Breast Cancer but Increase Risk of Adverse Effects, New Report Says. Press Release, September 15, 2009. Agency for Healthcare Research and Quality, Rockville, MD. Available at: http://www.ahrq.gov/news/press/pr2009/brcanmedpr.htm. Accessed May 24, 2010

130 Dawson SJ, Provenzano E, Caldas C. Triple negative breast cancers: Clinical and prognostic implications. Eur J Cancer. 2009 Sep; 45 Suppl 1:27-40.

131 Gangadhara S, Bertelli G. Long-term efficacy and safety of anastrozole for adjuvant treatment of early breast cancer in postmenopausal women. Ther Clin Risk Manag 2009; 5: 291–300.

132 Perez EA. Appraising Adjuvant Aromatase Inhibitor Therapy. The Oncologist 2006; 11:1058–1069.

133 Brédart A, Bottomley A. Treatment satisfaction as an outcome measure in cancer clinical treatment trials. Expert Rev Pharmacoecon Outcomes Res. 2002 Dec; 2(6):597-606.

134 Ruhstaller T, von Moos R, Rufibach K et al. Breast cancer patients on endocrine therapy reveal more symptoms when self-reporting than in pivotal trials: an outcome research study. Oncology 2009; 76: 142–148.

135 Leonard RCF, Lee L, Harrison ME. Impact of side-effects associated with endocrine treatments for advanced breast cancer: clinicians' and patients' perceptions. Breast 1996; 5: 259–264.

136 Fellowes D, Fallowfield LJ, Saunders CM, Houghton J. Tolerability of hormone therapies for breast cancer: how informative are documented symptom profiles in medical notes for "well-tolerated" treatments? Breast Cancer Res Treat 2001; 66: 73–81.

137 Kudachadkar R, O'Regan RM. Aromatase inhibitors as adjuvant therapy for postmenopausal patients with early stage breast cancer. CA Cancer J Clin. 2005 May-Jun; 55(3):145-63.

138 Ask a Patient. Available at: http://www.healthecho.com/Resources/Consumer_Information. Accessed May 20, 2010.

139 Love RR, Cameron L, Connell B. Symptoms associated with tamoxifen treatment in postmenopausal women. Arch Intern Med 1991; 151:1842-7.

140 Day R, Ganz PA, Costantino JP et al. Health related quality of life and tamoxifen in breast cancer prevention: A report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Clin Oncol 1999; 17:2659-2669.

141 Day R, Ganz PA, Costantino JP. Tamoxifen and depression: more evidence from the National Surgical Adjuvant Breast and Bowel Project's Breast Cancer Prevention (P-1) Randomized Study. J Natl Cancer Inst 2001; 93:1615-23.

142 Fallowfield L, Cella D, Cuzick J, et al. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. J Clin Oncol 2004; 22:4261–71.

143 Cella D, Fallowfield L, Barker P et al. Quality of life of postmenopausal women in the ATAC (''Arimidex'', tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for early breast cancer. Breast Cancer Res Treat 2006; 100: 273-284.

144 Fallowfield LJ, Bliss JM, Porter LS et al. Quality of Life in the Intergroup Exemestane Study: A Randomized Trial of Exemestane Versus Continued Tamoxifen After 2 to 3 Years of Tamoxifen in Postmenopausal Women With Primary Breast Cancer. Clin Oncol 2006; 24:910-917.

145 Ohsumi S, Shimozuma K, Ohashi Y et al. Health-related quality-of-life and psychological distress of breast cancer patients after surgery during phase III randomized trial comparing further tamoxifen with switching to

anastrozole after adjuvant tamoxifen for 1 to 4 years: N-SAS BC 03. Breast Can Res Treat 2011 May; 127(1):143-52.

146 Takei H, Ohsumi S, Shimozuma K et al. Health-related quality-of-life and psychological distress of breast cancer patients after surgery during phase III randomized trial comparing tamoxifen, exemestane, and anastrozole: N-SAS BC 04. Breast Can Res Treat 2006; 100(Suppl. 1): Abstract 4054.

147 van Nes JGH, Voskuil DW, van Leeuwen FE et al. Quality of life in relation to hormonal treatment of postmenopausal women in the Dutch tamoxifen Exemestane Adjuvant Multicentre (TEAM) trial. Cancer Res, 2009; Jan 15; 69 (Suppl 2); Abstract 21.

148 Whelan TJ, Goss PE, Ingle JN, Pater JL, Tu D, Pritchard K et al. Assessment of quality of life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women. J Clin Oncol 2005; 23:6931–40.

149 Muss HB, Tu D, Ingle JN et al. Efficacy, Toxicity, and Quality of Life in Older Women With Early-Stage Breast Cancer Treated With Letrozole or Placebo After 5 Years of Tamoxifen: NCIC CTG Intergroup Trial MA.17. J Clin Oncol 2008; 26:1956-1964.

150 Dixon JM, Renshaw L, Langride C et al. Anastrozole and letrozole: an investigation and comparison of quality of life and tolerability. Breast Cancer Res Treat, 2010 Feb; 125(3):741-9.

151 Thomas R. Examining Quality of Life Issues in Relation to Endocrine Therapy for Breast Cancer. Am J Clin Oncol (CCT) 2003; 26(4 Suppl 1): S40–S44.

152 Asmar L, Cantrell J, Vukelja J et al. A planned comparison of menopausal symptoms during the first year in 1000 patients receiving either exemestane or tamoxifen in a double-blind adjuvant hormonal study. Proc Am Soc Clin Oncol. 2004; 23:6. Abstract 516.

153 Francini G, Petroilo R, Montagnani A et al. Exemestane after tamoxifen as adjuvant hormonal therapy in postmenopausal women with breast cancer: effects on body composition and lipids. British Journal of Cancer 2006: 95, 153-158.

154 Jones S, Cantrell J, Vukelja S et al. Comparison of Menopausal Symptoms During the First Year of Adjuvant Therapy With Either Exemestane or Tamoxifen in Early Breast Cancer: Report of a Tamoxifen Exemestane Adjuvant Multicenter Trial Substudy. J Clin Oncol 2007; 25:4765-4771.

155 Schilder C, Eggens P, Seynaeve C et al. Neuropsychological functioning in postmenopausal breast cancer patients treated with tamoxifen or exemestane after AC-chemotherapy: Cross-sectional findings from the neuropsychological TEAM-side study. Acta Oncologica 2009; 48: 76-85.

156 Schilder CM, Seynaeve C, Beex LV et al. Effects of Tamoxifen and Exemestane on Cognitive Functioning of Postmenopausal Patients With Breast Cancer: Results From the Neuropsychological Side Study of the Tamoxifen and Exemestane Adjuvant Multinational Trial. J Clin Oncol 2010; 28:1294-1300.

157 Thomas R, Williams M, Marshall C et al. Switching to letrozole or exemestane improves hot flushes, mood and quality of life in tamoxifen intolerant women. British Journal of Cancer 2008: 98, 1494 -1499.

158 Mamounas EP, Jeong JH, Wickerham DL et al. Benefit From Exemestane As Extended Adjuvant Therapy After 5 Years of Adjuvant Tamoxifen: Intention-to-Treat Analysis of the National Surgical Adjuvant Breast and Bowel Project B-33 Trial. J Clin Oncol 2008; 26:1965-1971.

159 Boehm DU, Lebrecht A, Eckhardt T et al. Quality of life and adjuvant tamoxifen treatment in breast cancer patients. Eur J Cancer Care 2009; 18(5):500-506.

160 Crew KD, Greenlee H, Capodice J, et al. Prevalence of Joint Symptoms in Postmenopausal Women Taking Aromatase Inhibitors for Early-Stage Breast Cancer. J Clin Oncol 2007; 25:3877-3883.

161 Henry NL, Giles JT, Ang D et al. Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. Breast Cancer Res Treat 2008; 111:365-372.

162 Ochayon L, Zelker R, Kaduri L et al. Relationship Between Severity of Symptoms and Quality of Life in Patients With Breast Cancer Receiving Adjuvant Hormonal Therapy. Oncol Nurs Forum. 2010 Sep 1; 37(5):E349-58.

163 Mouridsen H, Sun Y, Gershanovich M et al. Superiority of Letrozole to Tamoxifen in the First-Line Treatment of Advanced Breast Cancer: Evidence from Metastatic Subgroups and a Test of Functional Ability. The Oncologist 2004; 9: 489-496.

164 Cella DF, Tulsky DS, Gray G et al. The functional assessment of cancer therapy scale: development and validation of the general measure. J Clin Oncol 1993 : 11, 570–579.

165 Brady MJ, Cella DF, Mo F et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. J Clin Oncol 1997 :15:974-986.

166 Fallowfield LJ, Leaity SK, Howell A et al. Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B. Breast Cancer Research and Treatment 1999; 55: 189–199.

167 Hilditch JR, Lewis J, Peter A et al: A menopause-specific quality of life questionnaire: Development and psychometric properties. Maturitas1996:24:161-175.

168 Carlsson M, Arman M, Backman M et al. Evaluation of Quality of Life/Life Satisfaction in Women with Breast Cancer in Complementary and Conventional Care. Acta Oncologica 2004 Vol. 43, No. 1, 27-34.

169 Jansen SJ, Kievit J, Nooij MA, et al. Patients' preferences for adjuvant chemotherapy in early-stage breast cancer: is treatment worthwhile? Br J Cancer 2001; 84:1577–85.

170 Bosnjak S, Radulović S, Nesković-Konstantinović Z, Mitrović L. Patient Statement of Satisfaction With Antiemetic Treatment Is Related to Quality of Life. Am J Clin Oncol (CCT) 2000:23(6): 575–578.

171 Cohen G. Age and health status in a patient satisfaction survey. Soc Sci Med 1996; 42: 1085–1093.

172 Geitona M, Kyriopoulos J, Zavras J et al. Medication use and patient satisfaction: a population based survey. Fam Pract 2008; 25: 362–369.

173 Atkinson MJ, Caldwell L. The differential effects of mood on patients' ratings of life quality and satisfaction with their care. Journal of Affective Disorders 1997:44: 169–175.

174 Gray R, Rofail D, Allen J, Newey T. A survey of patient satisfaction with and subjective experiences of treatment with antipsychotic medication. Journal of Advanced Nursing, 2005: 52(1), 31–37.

175 Chen K, Chiou CF et al. Patient satisfaction with antihypertensive therapy. Journal of Human Hypertension 2005:19, 793-799.

176 Hoffman RM, Hunt WC, Gilliland FD et al. Patient Satisfaction with Treatment Decisions for Clinically Localized Prostate Carcinoma. Results from the Prostate Cancer Outcomes Study. Cancer 2003;97:1653–62.

177 Sanda MG, Dunn RL, Michalski J et al. Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors. N Engl J Med. 2008 Mar 20;358(12):1250-61.

178 Bolge SC, McDonnell DD, Chen A, Wan GJ. Patient satisfaction with extended release tolterodine or oxybutynin in overactive bladder. Curr Med Res Opin. 2007 Aug;23(8):1903-12.

179 Bultman DC, Svarstad BL. Effects of pharmacist monitoring on patient satisfaction with antidepressant medication therapy. J Am Pharm Assoc (Wash). 2002 Jan-Feb;42(1):36-43.

180 Biderman A, Noff E, Harris SB, Treatment satisfaction of diabetic patients: what are the contributing factors? Fam Pract. 2009 Apr;26(2):102-8. Epub 2009 Mar 2.

181 Nicolucci A, Cucinotta F, Squatrito S et al. For the QuoLITy Study Group. Clinical and socio-economic correlates of quality of life and treatment satisfaction in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis 2009; 19: 45–53.

182 Brod M, Valensi P, Shaban JA et al. Patient treatment satisfaction after switching to NovoMix® 30 (BIAsp 30) in the IMPROVE™ study: an analysis of the influence of prior and current treatment factors. Qual Life Res. 2010 Nov; 19(9):1285-93. Epub 2010 Jul 4.

183 Westaway MS, Rheeder P, Van Zyl DG, Seager JR. Interpersonal and organizational dimensions of patient satisfaction: themoderating effects of health status. Int JQualHealth Care 2003; 15: 337–344.

184 Basch E, Artz D, Dulko D et al. Patient online self-reporting of toxicity symptoms during chemotherapy. J Clin Oncol. 2005; 23 (15): 3552–3561.

185 Chen X, Siu LL. Impact of the media and the Internet on oncology: survey of cancer patients and oncologists in Canada. J Clin Oncol 2001; 19:4291–4297.

186 Jenkins V, Fallowfield L, Saul J. Information needs of patients with cancer: results from a large study in UK cancer centres. Br J Cancer 2001; 84:48–51.

187 Fogel J, Albert SM, Schnabel F et al. Use of the Internet by Women with Breast Cancer. J Med Internet Res 2002; 4(2):e9.

188 Eysenbach G. The Impact of the Internet on Cancer Outcomes. CA Cancer J Clin 2003; 53:356–371.

189 Monnier J, Laken M and Carter C. Patient and caregiver interest in Internet-based cancer services. Cancer Pract. 2002, 10(6): 305-310.

190 Meric F, Bernstam EV, Mirza NQ et al. Breast cancer on the world wide web: cross sectional survey of quality of information and popularity of websites. BMJ 2002; 324: 577-581.

191 Shon J, Musen MA. The low availability of metadata elements for evaluating the quality of medical information on the World Wide Web. Proceedings of the AMIA Symposium, 1999; 945–949.

192 Berland GK, Elliott MN, Morales LS, et al. Health information on the Internet: accessibility, quality, and readability in English and Spanish. JAMA 2001; 285:2612–2621.

193 Eysenbach G, Till JE. Ethical issues in qualitative research on Internet communities. BMJ 2001; Nov 10; 323(7321):1103-5.

194 Shuster LT, Rhodes DJ, Gostout BS et al. Premature menopause or early menopause: long-term health consequences. Maturitas. 2010; 65, 161-166.

195 Cuzick J, Sestak I, Cella D, Fallowfield L. Treatment-emergent endocrine symptoms and the risk of breast cancer recurrence: a retrospective analysis of the ATAC trial. Lancet Oncol 2008; 9: 1143–48.

196 Sestak I, Sapunar F, Cuzick J. Aromatase Inhibitor-Induced Carpal Tunnel Syndrome: Results From the ATAC Trial. J Clin Oncol 2009; 27:4961-4965.

197 Neuropathy. Canadian Neuropathy Association. Available at: http://canadianneuropathyassociation.org/pages/neuropathy.php. Accessed May 29, 2010

198 Neuropathy. The Neuropath Association. Available at: http://www.neuropathy.org/site/PageServer?pagename=About_Facts. Accessed May 29, 2010

199 Lash TL, Fox MP, Westrup JL, Fink AK, Silliman RA. Adherence to tamoxifen over the five-year course. Breast Cancer Res Treat 2006; 99:215–20.

200 ATAC Trialists' Group. Comprehensive side effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. Lancet Oncol 2006, 7:633-643.

201 Jenkins V, Shilling V, Fallowfield L et al. Does hormone therapy for the treatment of breast cancer have a detrimental effect on memory and cognition? A pilot study. Psychooncology 2004; 13:61–66.

202 Bender CM, Sereika SM, Ryan CM et al. Memory impairments with anastrozole versus tamoxifen therapy in women with early stage breast cancer. Breast Cancer Res Treat 2005; 94(suppl 1):6074a.

203 Coates AS, Keshaviah A et al. Five Years of Letrozole Compared with Tamoxifen as Initial Adjuvant Therapy for Postmenopausal Women with Endocrine-Responsive Early Breast Cancer: Update of Study BIG 1-98. J Clin Oncol. 2007 Feb 10; 25(5): 486-92.

204 Simpson D, Curran MP, Perry CM. Letrozole: a review of its use in postmenopausal women with breast cancer. Drugs 2004; 54:1213–1230.

205 The BIG 1-98 Collaborative Group. Letrozole therapy alone or in sequence with tamoxifen for women with breast cancer. N Engl J Med. 2009 Aug 20; 361(8): 766-76.

206 Coleman R, Banks LM, Girgis S et al. Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. Lancet Oncol 2007; 8: 119–27.

207 Coombes RC, Kilburn LS, Snowdon CF et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet 2007; 369: 559–570.

208 Bliss JM, Kilburn LS, Coleman RE et al. Disease related outcome with long term follow-up: An updated analysis of the Intergroup Exemestane Study (IES). Cancer Res. 2009; 69 (24 Suppl 3). Abstract 12.

209 FDA: Drug Safety Communication: Safety update for osteoporosis drugs, bisphosphonates, and atypical fractures. Available at:
http://www.fda.gov/Drugs/DrugSafety/ucm229009.htm. Accessed Oct.30, 2010