LONGITUDINAL EPIDEMIOLOGY OF PAIN SEVERITY AND INTERFERENCE AMONG WOMEN WITH METASTATIC BREAST CANCER

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ABSTRACT

LIANA CASTEL: Longitudinal Epidemiology of Pain Severity and Interference among Women with Metastatic Breast Cancer
(Under the direction of Katherine Hartmann)

Knowledge is limited about risk factors for cancer pain experienced over the course of disease in specific tumor types. In this study, we assessed pain hazards using data originally collected over 51 weeks in a clinical trial among 1,124 women with metastatic breast cancer; pain was measured by the Brief Pain Inventory (BPI) severity and interference with daily living 0-10 subscales.

Under a continuous time assumption, we conducted univariate (per-cutpoint) and multivariate (cutpoints 3, 4, 5, 6, and 7 on the BPI) proportional hazards analyses to estimate effects of baseline characteristics on pain hazards. For the severity scale, compared with Caucasian race, non-Caucasian race was associated with 2.29 times the hazard of reaching severity cutpoint 7 versus 1.38 for cutpoint 3, all other covariates held constant. For the interference scale, compared with active baseline Eastern Cooperative Oncology Group (ECOG) status, restricted baseline ECOG status was associated with 2.97 times the hazard of reaching interference cutpoint 7 versus 2.00 for cutpoint 3.

Under a categorical (interval-censored) time assumption, we used piecewise exponential models to estimate associations of baseline and time-dependent characteristics with "survival" rates for not yet reaching a score of 7 or above on each subscale, per 80-day interval. Estimated survival rates at the first interval were 0.92 for Caucasian women versus 0.80 for non-Caucasian women; for the interference scale, these rates were 0.80 versus 0.70,

respectively. In subsequent intervals, rates declined similarly for Caucasian and non-Caucasian women, but for both pain outcomes, the cumulative survival rate for Caucasians in the last interval was still higher than that of non-Caucasians in the first interval.

In confirming associations of ECOG performance status (both as a baseline and time-dependent covariate) and race with pain hazards over time in metastatic breast cancer, our findings inform individualized prognoses for pain outcomes according to baseline patient attributes. Early intervention and more aggressive pain management strategies can be tailored to these personalized prognoses over the course of treatment, to delay first occurrence of higher pain scores among those at greatest risk. Future research should specifically target potential sources of racial disparities in cancer pain.

DEDICATION

This work is dedicated to the memory of Dr. Harry Guess. As my advisor and Committee Chair, and also as my teacher and supervisor, Harry was a true mentor. He gave me enthusiastic support and encouragement, as well as honest and practical suggestions to improve my work. Harry had already achieved great advancements in public health during his career. Still, throughout his devastating struggle with lung cancer, he gave priority to helping me with my dissertation. His remarkable courage, intelligence, collegiality, and dedication set an example for me in my work and in my life.

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This work could not have been completed without the constant love, understanding, inspiration, advice, and support that I have been so fortunate to receive from my husband Emmanuel Castel, from my parents, Drs. Gaston and Susan DesHarnais, and from my librarian sister Miriam DesHarnais.

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LIST OF ABBREVIATIONS

AHCPR	Agency for Health Care Policy and Research (new name: AHRQ)
AHRQ	Agency for Healthcare Research and Quality
ANOVA	analysis of variance
APS	American Pain Society
BPI	Brief Pain Inventory
CI(s)	confidence interval(s)
COX-2	cyclooxygenase-2
CRF	case report form
CRO	contract research organization
CYP	cytochrome p450
DAG	directed acyclic graph
DIF	differential item functioning
DME	drug-metabolizing enzyme(s)
ECOG	Eastern Cooperative Oncology Group
EM	expectation maximization
FACT-B	Functional Assessment of Cancer Therapy – Breast
FACT-G	Functional Assessment of Cancer Therapy – General
GEE	generalized estimating equation
HR(s)	hazard ratios
HRQoL	health-related quality of life
ISI	Institute for Scientific Information
ITT	intent-to-treat

KM	Kaplan Meier
KPS	Karnofsky performance status
MeSH	medical subject heading
MID	minimal(ly) important difference
MS1	Manuscript 1
MS2	Manuscript 2
NCI	National Cancer Institute
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory
NRS	numeric rating scale
PRO	patient-reported outcome
QC	quality control
RCT	randomized controlled trial
SEER	Surveillance, Epidemiology and End Results
SRE	skeletal related event
VAS	visual analogue scale
WHO	World Health Organization

CHAPTER I

INTRODUCTION

As studies of both cancer-specific patient-reported outcomes (PROs) and of palliative care have become more common over the past few decades, researchers have devoted increasing efforts toward understanding and management of pain. Pain is a key dimension of the degradation of quality of life associated with cancer,[1,2] and an important element of suffering associated with cancer metastases, the process by which, as disease progresses, the spread of cancerous cells beyond the original site can lead to disruption of many bodily systems. Since metastasis is the most severe and common life-threatening complication arising from cancer, its exacerbation by suffering constitutes an important factor in both palliative efficiency and disease progression.[3]

Several key background elements should be considered in the study of cancer pain and treatment outcomes. Due to ongoing and increasing recognition of the importance of pain as an outcome (pain is sometimes called the "fifth vital sign"), a large body of literature has emerged comprising cancer pain incidence and prevalence, risk factors for pain, the effectiveness of various analgesic interventions, and the construction and testing of algorithms for pain management strategies based on available evidence. These study designs range from observational, experimental, meta-analytic, and measurement/validation studies. Key reviews have advocated for studying pain using tumor-specific data collected at repeated assessments over time.[4-6] There is evidence that analgesic therapy is often inadequate for

patients in general,[7] but also that the burden of pain and inadequate analgesia is greater among Black and Hispanic patients as compared with Caucasian patients.[8] In addition, interpretation and translation of pain research findings often rely on grading pain severity, using numeric cutpoints to demarcate categories of severity such as mild, moderate, or severe pain on a numeric rating scale. Existing methodological studies in this area cite the need for further study to explore cancer-specific pain severity cutpoints in detail.[9-12]

The present study, conducted under approval from the University of North Carolina at Chapel Hill Institutional Review Board (see Appendix A), addresses the needs for tumor-specific information about patients' experiences and risk of pain over time, assessment of racial differences in experiences and risk of pain over time, and exploration of pain severity cutpoints on a commonly used pain rating scale. We apply methods for assessing risks over time, as well as the contributions of predictive baseline and time-dependent clinical and demographic covariates, to clinical trial data from 1,124 breast cancer patients collected over at least 51 weeks. The two manuscripts prepared for fulfillment of the Epidemiology doctoral program requirements are as follows:

Manuscript 1: We conducted proportional hazards analyses for reaching different thresholds of pain on the Brief Pain Inventory (BPI) severity and interference scales over time, comparing which sets of clinical and demographic baseline predictors affect hazards of reaching different thresholds of pain as defined by cutpoints on the 0 – 10 severity and interference scales. Patients reaching the intensity cutpoints of 3, 4, 5, 6, and 7 or above on each scale were the outcomes of interest in predictive modeling to analyze each cutpoint separately, and then all cutpoints together, exploring interactions between covariates and cutpoints. Time-to-event was treated as continuous in these analyses. Our findings provide

descriptive epidemiologic information about pain hazards over time among patients with metastatic breast cancer, the effect of using different intensity cutpoints on these scales, and the relationship between the pain severity and interference BPI scales with regard to baseline covariates as risk factors. This study addresses Aims 1 and 2 of the dissertation (see Section IIIA).

Manuscript 2: We fit models to accommodate interval-censored data (categorical time-to-event), predicting time to first reaching a pain severity or interference score of 7 or above on the 0-10 BPI scales. We estimated the associations of both baseline and time-dependent clinical and demographic characteristics with hazards for the outcomes. We investigated the hypothesis that, as compared with their Caucasian counterparts, non-Caucasian patients would have higher hazards of pain severity and pain interference in daily functions. This study addresses Aims 2, 3, and 4 of the dissertation (see Section IIIA).

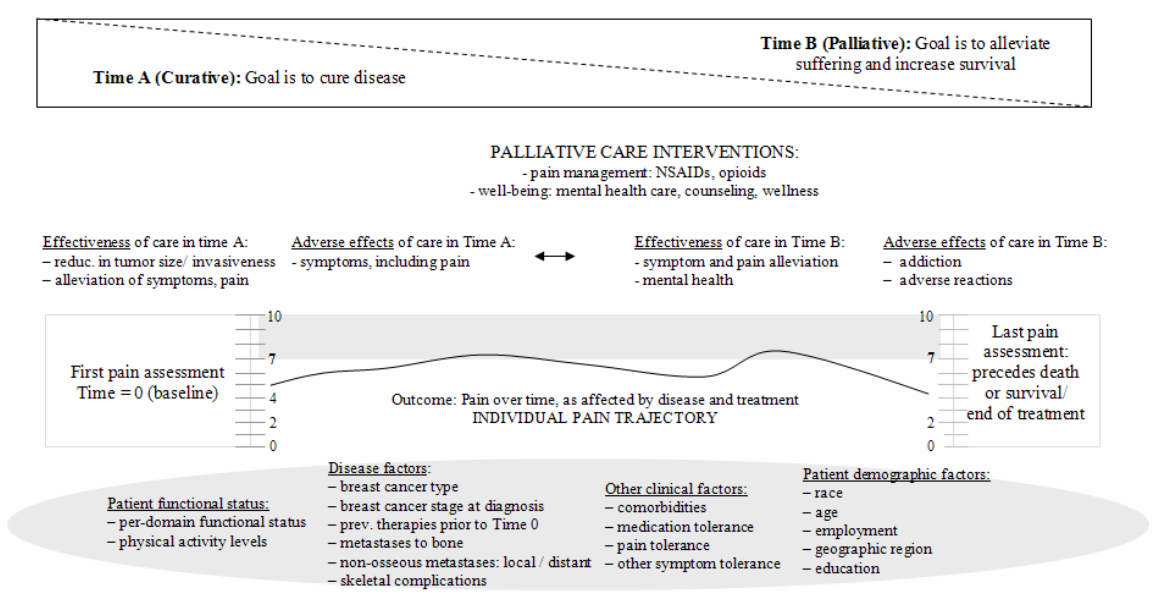
CHAPTER II

BACKGROUND

A. Conceptual framework

The course of a given patient's cancer pain over the time of cancer and pain treatment involves factors related to disease etiology, measurement of PROs, psychology and characteristics of both patients and physicians, societal and systemic characteristics, and the effectiveness of clinical interventions. Patient preferences, medication adherence, and judgments/perceptions shape the experience of pain over the course of cancer. Pain treatment is also affected by providers' judgments/perceptions, as well as their levels of adherence to relevant clinical practice guidelines. The conceptual model shown in Figure 1 explores the interaction of factors with the potential to influence pain. These factors exist on many levels, and include characteristics of: patients, providers, patient-provider communication and decision making, disease, health care systems, and geographic and sociocultural environments, traditions, and prejudices. The specific constellation of factors that affect one person's experience of pain is certainly unique, but identifying predictive patterns among factors that affect the risk of specific pain outcomes in specific populations over time can enhance our knowledge and ability to manage pain successfully.

Figure 1. Conceptual framework: focus of care, sample trajectory



Note: Curative/Palliative portion of schema (top of diagram) adapted from a World Health Organization (WHO) report.[13]

A hypothetical trajectory, or course of pain on a 0-10 scale over time for one patient, is also illustrated in Figure 1 (labeled "outcome: Pain over time…"). Patient functional status, disease status, and demographic characteristics are the key independent variables of concern in the present investigation, and are shown in the shaded oval portion of Figure 1 as they fit into the conceptual schema of pain experienced over time. Race was of importance in the present investigation and in this conceptual model because of its complexity as a construct. In a pragmatic sense, the minority status variable is of value in predictive modeling because it is often a consistent predictor of worse pain outcomes. However, simply adding evidence that outcomes differ by race or ethnicity is only the first step. To improve outcomes, we must address the sources of the disparities we observe. These sources of pain disparities by minority status are complex, simultaneously involving many of the factors shown in the

conceptual model above. The model is of use in interpreting findings of differences according to racial/ethnic classifications.

Also of importance in the schema is the concept of cutpoints to define categories of pain intensity. The shaded portion above the 7 cutpoint in the schema illustrates that a person may, through the course of disease, experience degrees of pain that could be dichotomously defined as severe or not severe, using 7 as a cutpoint for this categorization. Such classifications of pain outcomes are useful in studying outcomes, but should be studied further in the context of clinically meaningful differences, sensitivity analyses, and scale validation.

As context for understanding treatment and patient and provider decision making over time, it is important to consider the concept of a curative-palliation shift over time. Depending on the type of cancer and its progression, disease may become so advanced that providers and perhaps patients direct their focus more toward symptom palliation and increasing survival than toward curing the cancer. Past research has shown that patients have higher expectations of survival and treatment benefits than their providers.[14-17] Effective pain management requires that both the patient and physician share similar goals for palliative treatment, and both be willing to implement the appropriate palliative measures. Palliation can co-exist with curative treatment, and current guidelines encourage this coexistence.[5,18] Because changes in pain can be important signals of disease progression that call for adjustments in intervention, treatment strategies that use signs other than pain to evaluate disease progression are important in ensuring that pain treatment does not decrease treatment effectiveness. When they follow evidence-based clinical practice guidelines and use

information learned from epidemiologic studies, providers are taking into account patient characteristics found to affect pain over time on a population level.

The conceptual framework presented is used to interpret our findings in the context of past research, and in forming recommendations for future practice and research, especially with regard to differences in pain outcomes that are found to vary according to patient demographic or clinical characteristics.

B. Substantive background

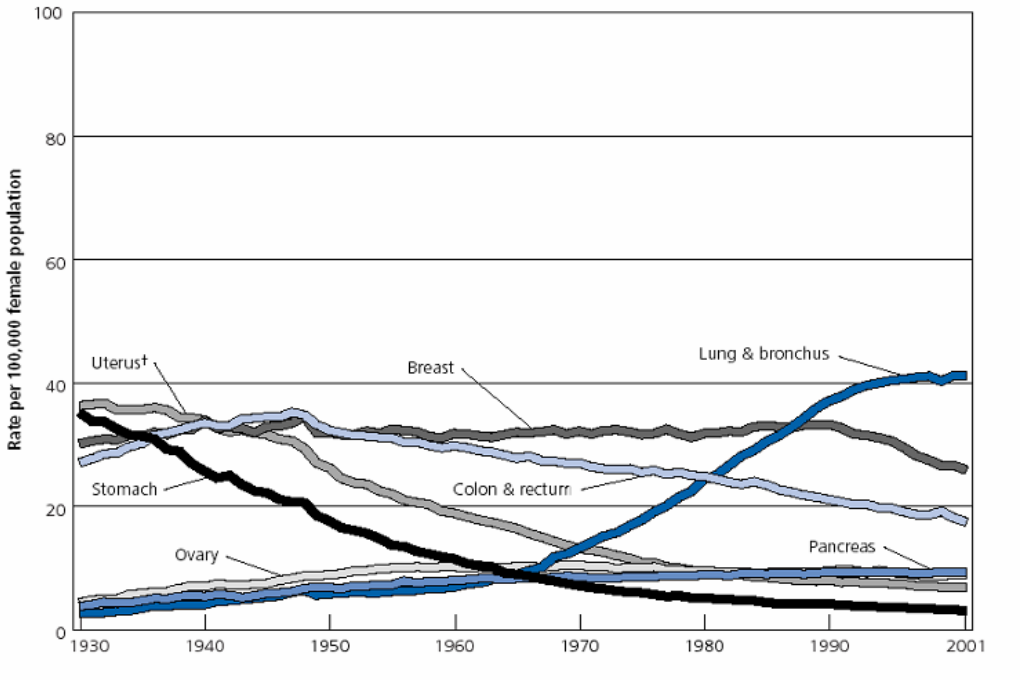
This section provides background information that synthesizes and draws upon existing literature, covering the following topics: incidence and mortality of breast cancer, prevalence of cancer pain, measurement /assessment of cancer pain, establishment of severity cutoffs for the Brief Pain Inventory, measurement/ assessment of cancer severity, pain associated with disease or therapeutic interventions, racial disparities in pain, and therapeutic interventions for cancer pain. Strategies for gathering, selecting, and assessing the most relevant literature follow in Section C: Literature search strategies. A critical evidence-based review of the sources judged as most comprehensive, influential, and timely follow in the subsequent section (Section D: Critical review of literature).

Incidence and mortality: breast cancer

Cancer incidence overall in the United States (source: National Cancer Institute) appears to have risen and is projected to rise in future years, especially among the elderly, rising in those aged 65 or older from incidence of approximately 1650 cases per million in 1974 to 2100 cases per million in 1996.[19] As shown in Figure 2 (age-adjusted cancer death rates in US females over the past 70 years), breast cancer is second only to lung cancer among the

tumor types with highest mortality rates as of 2001. Our focus in the present study on breast cancer addresses an important tumor type.

Figure 2. Age-Adjusted Cancer Death Rates,* Females by Site, US, 1930-2001



*Per 100,000, age-adjusted to the 2000 US standard population.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung & bronchus, colon & rectum, and ovary are affected by these coding changes.

Source: American Cancer Society. *Facts and Figures 2005.* Atlanta: American Cancer Society, Inc.

Prevalence of cancer pain

A common presentation of cancer pain associated with bone metastases in women with metastatic breast cancer includes the following characteristics: (a) pain described as dull and aching, and (b) pain that is well-localized to the metastatic site.[18] Breast cancer related pain may also take the form of epidural spinal cord compression, brachial plexopathy (radiating shoulder pain), postherpetic neuralgia (shock-like pain associated with skin lesions), and other painful syndromes.[18] Disease progression in the form of metastases emerges

consistently as a major determinant of pain, including severity and progression. The site of metastases and even type of bone to which the cancer metastasizes affect pain. Metastases to bone affect pain differently from metastases to soft tissue, especially brain. Pain associated with specific tumor types depends on (a) the pain definition used, (b) patterns of metastases, (c) different contributions of societal and cultural factors (e.g., stigma associated with different tumor types), and (d) tumor-specific prevalences of different types of pain (e.g., neuropathic, somatic).

Epidemiologic studies of pain prevalence can be designed to examine not only levels of pain severity and interference with daily functions, but also frequency and recurrence of these outcomes. With regards to the prevalence of cancer pain in general (i.e., not tumor-specific), studies have estimated that chronic or recurrent pain affects about 30% of all patients with cancer, and about 60 to 90% of patients with advanced cancer.[20,21] In an Eastern Cooperative Oncology Group (ECOG) study of the adequacy of pain relief among over 1300 outpatient metastatic cancer patients, 67% reported having pain or taking analgesics, and 36% reported pain severe enough to impair their functional status. Among those who took analgesics (46%), nearly half of those patients reported that they were not being given adequate analgesic therapy.[7] Both severe pain and inadequately treated pain emerge as problems of particular concern among patients with cancer. Pain associated with specific tumor types depends on (a) the pain definition used, (b) patterns of metastases, (c) different contributions of societal and cultural factors (e.g., stigma associated with different tumor types), and (d) tumor-specific prevalences of different types of pain (e.g., neuropathic, somatic).

The persistent problems of inadequate analgesic treatment and severe pain are recurrent themes in studies of cancer pain and its treatment. Examples of psychological, quality of life, and financial consequences of inadequately treated pain are well illustrated by the American Pain Society at: http://www.ampainsoc.org/ce/npc/tables/5.htm in patterns of clinical manifestations known to result from physiological stress responses to pain; for example, musculoskeletal pain is known to induce stress responses such as muscle spasm and impaired muscle mobility and function. These stress responses may clinically manifest as weakness, fatigue, or immobility.[22,23] Inadequate analgesic treatment of cancer pain was well-documented in a study of 1308 cancer outpatients at 54 treatment sites.[7] Sixty-seven percent of the patients interviewed reported pain sufficient to require daily analgesics, and 36% reported that the pain limited their ability to function. Only 42% of those with pain reported receiving sufficient pain relief. Several other studies documented that pain associated with terminal illness was often undertreated,[24-27] and that patients who desired more pain treatment had poorer physical functioning, more depressive symptoms, and were more likely to be minority.[28]

Measurement/assessment of cancer pain

The fact that pain has long been considered to be a subjective phenomenon[29] has often provoked a reaction that its subjectivity may somehow prevent its accurate quantitative measurement. Given that seemingly objective phenomena such as blood pressure (or any measurements taken from the patient in any manner except linguistic communication) may (a) be influenced by such subjective states as the patient's mood while their blood pressure is being measured, and (b) still be open to interpretation error, the subjectivity of patient-reported pain should not limit its usefulness. Differential item functioning (DIF) is a potential

issue because patients may report scores other than their true score (over- or under-reporting of pain). Although assessment for DIF is beyond the scope of this analysis, implications of such inaccuracies are discussed in the section on potential bias, confounding, and effect modification.

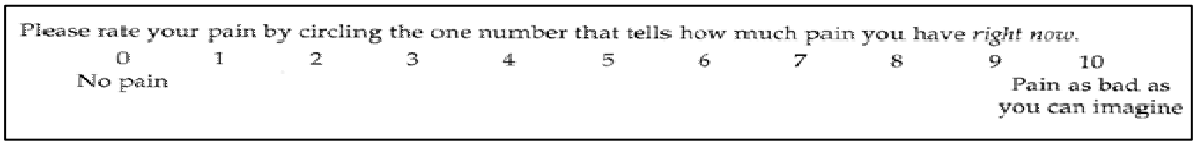
As is the case with measurement of all PROs including quality of life, satisfaction, or psychological states, a good measure of pain will possess properties of internal and external validity, and can thus provide accurate quantitative information for the purposes of comparing subgroups of patients and generalizing findings appropriately to larger populations. It is important when assessing pain to keep in mind the potential influences of bias on patient responses. Patients may underreport or overreport the pain they experience. Although underestimation of pain is more a problem in retrospective studies involving spontaneous patient reports,[30] it is still possible that in the present study, patients may underreport pain (there is more evidence for underreporting, rather than overreporting, being a likely problem). Based on cultural views, some patients may believe that pain is a spiritual or religious test of their faith, or believe that it is wrong to take or become addicted to opioids. Fear of addiction has been seen in about a third of terminally ill patients.[28] Patients may therefore refuse to report their pain or accept palliative treatment.[31] Patient reluctance can affect both solicited and unsolicited reports of pain, leading to underestimates of pain incidence, prevalence, and severity in retrospective studies.[30] Prospective pain assessments can help to reduce this bias.[32]

Despite the drawbacks of pain measurement and threats to its validity, the effectiveness of analgesic interventions is most effectively gauged by using patient-reported pain data. We can compare the effectiveness of various interventions more systematically as data collection

and measurement instruments are used consistently and validated more extensively in clinical practice and research. Several scales are routinely used.

Visual analogue scale (VAS) and numeric rating scale (NRS) measures usually assess pain severity on a scale from 0 to 10, with 0 being "no pain" and 10 being "worst pain I can imagine". The instructions preceding the scale may say "Place a mark on the scale according to how you feel right now", or "indicate the intensity of the worst pain you felt over the past 2 weeks". According to the American Pain Society Clinical Practice Guideline for the Management of Cancer Pain in Adults and Children,[18] NRS measures are among the most common, valid, and reliable measures used to assess cancer pain intensity, and are preferred by patients over VAS measures. An example of a question from the Brief Pain Inventory,[33] or BPI (a classic NRS measure created by Charles Cleeland) is shown in Figure 3. A reprint of the relevant sections of the BPI is included as Appendix B.

Figure 3. Excerpt from the Brief Pain Inventory (BPI) severity subscale.



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The concepts of intensity and severity are sometimes used synonymously in the field of pain research, but for the BPI, both severity and interference fall under the category of pain intensity, which is measured by the entire BPI. The BPI has been administered and assessed for validity in several languages including Spanish, French, Japanese, Chinese, Italian, Hindi, German, Greek, and Vietnamese.[34-40]

Patients with cancer may experience pain at multiple sites on the body, separately or concurrently, and their pain may be occurring through different or multiple mechanisms.

Attempts have been made to categorize patterns of pain, such as continuous, movement-related, acute, and spontaneous breakthrough pain.[41] Breakthrough pain is defined as a brief flare-up of severe pain that occurs even as the patient is being treated regularly with pain medication; this type of pain usually comes on quickly and may last from a few minutes to an hour. Both numeric and non-numeric categorizations and characterizations of pain and changes in pain are key cues for making both disease- and pain-treatment decisions. Pain-related considerations specific to different types of cancer, however, should also be included in understanding and treating pain. Some pain syndromes are tumor-specific manifestations of local or distant metastases, while others reflect diffuse effects (such as metastases to blood or lymphatic systems). Any form of pain mentioned may not be related to disease at all, but rather have been brought about as a secondary effect of diagnostic procedres, cancer treatment such as surgery, radiation, or chemotherapy, infection, or immobility.

Tumor-specific measures of cancer pain may offer information more pertinent to patients with a given tumor type than information gained from other types of measures, which may be cancer-specific versus non-disease-specific, tumor-specific versus non-tumor-specific, and may measure pain alone or as a component of quality of life. For example, there is one item "I have pain" that is a component of the Physical Well-Being subscale of the FACT-G (Functional Assessment of Cancer Therapy – General, i.e., not tumor specific), but in the tumor-specific version of this quality of life measure (the FACT-B, a breast cancer-specific version of the FACT), the "I have pain" item still exists, but there is also the item "I have certain parts of my body where I experience significant pain" as a component of the Additional Concerns subscale. Tumor-specific measures structured in this way retain the

validity and reliability of the original "core" measure, while adding information pertinent to detriments experienced in specific subpopulations as a result of their disease.

Adequacy of Analgesic treatment

Successful pain management requires both responsive and even pre-emptive analgesic treatment to avoid worse pain outcomes,[42] based on ongoing gathering and use of disease, clinical, and patient-reported information available to the clinician. In addition to defining severity of pain, capturing the concept of inadequate pain treatment is important in order to accurately measure pain as an outcome; this importance becomes clear when one considers the previously mentioned possible negative psychological, quality of life, and financial consequences of inadequately treated pain. One method of ascertaining whether inadequate analgesic treatment is a problem for a given patient is to ask the patient whether they feel they are receiving sufficient pain relief. Another method is to measure pain before and after analgesic administration to assess whether the analgesic was associated with pain reduction.

Brief Pain Inventory Cutoffs

Classifying pain into severity categories according to cutpoints on a 0-10 numeric rating scale is of extensive use in research and clinical practice. Cutpoints are used to drive treatment decisions, develop practice guidelines, and determine effectiveness of interventions. Where the cutoff point is set for severe pain also affects descriptive epidemiology, including etiological reports on longitudinal cancer pain, as well as point prevalence estimates in populations. When a patient reaches a level of pain considered severe, the event is often considered a "treatment failure" because successful pain management should have prevented the patient from first reaching severe pain. It is important to note that because severity cutpoints are used in decision making and indicate treatment

failure, there is debate over the classification of severe pain; in practice even a score of 5 may be considered severe, and thus a trigger for palliative intervention.

In their 1995 study, Cleeland and colleagues explored the utility of dividing pain into three categories based on cutoffs on the BPI NRS measure: mild pain was defined as a score of 1-4, moderate pain as 5-6, and severe pain as 7-10.[11] These pain severity cutoffs were used to establish a basis for later work on clinically meaningful changes in pain that could indicate therapeutic effectiveness. Farrar and colleagues have conducted several studies to quantify clinically meaningful changes on 0-10 NRS measures. In their 2003 study of the such a measure using receiver operating characteristic methods, "the best cut-off points were determined to be: 33% for the percent pain intensity difference; > or =2 for the raw pain intensity difference on a 0-10 numeric rating scale; > or =2 (i.e., moderate or better) for pain relief; > or =33% for the percent maximum total pain relief; and > or =2 (good or better) for global medication performance."[43] The aim of using cutoffs on a NRS to define severe pain is to initiate palliative intervention when it is needed. The present study addresses the need cited for further exploration and definition of pain severity cutpoints.[9-12] By exploring the effects of different severe pain cutoffs on population-level estimates of risk of severe pain, the present study will help to either justify or suggest changes to the cutoff points most commonly used in clinical practice today.

Pain associated with disease or therapeutic interventions

Disease-related pain

Cancer pain associated with the disease per se, and not with treatments (discussed below) can result from conditions caused by the tumor or cancerous cells including the following: blocked blood vessels causing poor circulation, bone fracture from metastasis to bone,

infection, inflammation, psychological or emotional problems, or nerve pain due to pressure exerted by a tumor.[44] In breast cancer patients with metastases to bone, common cancer pain presentations include spine metastasis that may impinge on nerve roots and produce radicular pain.[18] In addition, metastasis to the base of the skull may produce headache, pain associated with head movement, and pain in the face, shoulder, and neck.[18] Disease processes alone have the potential to cause severe and/or persistent pain through the mechanisms described or through additional mechanisms such as immobility or infection, especially as severity increases and the cancer metastasizes beyond its primary site.

Specific treatment recommendations

Standard clinical interventions for breast cancer depend on disease severity upon presentation (as indicated by stage at diagnosis) and presence versus absence of metastases. Treatment strategies usually involve a combination and/or succession of combinations of surgery, radiation, chemotherapy, or hormonal treatment (including tamoxifen). Treatment strategies as presented are recommendations of the National Cancer Institute (NCI), based on synthesis of information gained from past clinical trials; it is important to note that clinical trials are also currently underway to compare different recommended strategies; the NCI guidelines reflect present knowledge, which is constantly being built upon.

For treatment purposes, breast cancers fall into the following main categories: (A) ductal carcinoma in situ, (B) lobular carcinoma in situ, (C) stages I, II, IIIA, and operable IIIC breast cancer, and (D) stage IIIB, inoperable IIIC, IV, recurrent, and metastatic breast cancer. For ductal carcinoma in situ (a non-invasive, precancerous condition that may progress to a different, invasive form), the NCI recommends the following three strategies: (a) breast-conserving surgery and radiation therapy, with or without tamoxifen, (b) total mastectomy

with or without tamoxifen, and (c) breast-conserving surgery without radiation therapy. For lobular carcinoma in situ, the following strategy is recommended: (a) observation after diagnostic biopsy, (b) tamoxifen to decrease the incidence of subsequent breast cancers, and (c) bilateral prophylactic total mastectomy, without axillary node dissection. For the other categories of breast cancer described above (Stage I, II, IIIA, and operable IIIC breast cancer, as well as stage IIIB, inoperable IIIC, IV, recurrent, and metastatic breast cancer) the most common form of treatment is what is called a "multimodality approach", in which a combination of palliative treatments, surgery with adjuvant chemotherapy, radiation, and hormonal therapies may all be given at once, or tried in pairs, multiples, or different orders. The effectiveness of the various orders of treatment and choices of treatment are being evaluated in various clinical trials, but at this time the combinations and sequences of these therapies are determined by the treating physician based on information and disease status throughout the course of treatment. The therapeutic interventions described above are largely for curative intent, although interventions with palliative intent can be integrated into these strategies at all points on the continuum of care, as illustrated in the conceptual model shown in Figure 1.

Treatment interventions and pain

Each type of therapeutic intervention may be examined with regard to its potential acute or chronic pain-related side effects. Surgery, radiation, chemotherapy, and hormonal therapy are each commonly used to treat breast cancers. The goal of surgery is to excise cancerous cells, in an aim to remove them from the body. Post-operative pain related to surgery is normally categorized as acute rather than chronic, and may involve swelling, soreness, or disruption of normal functioning; for example, post-operative pain following surgery on the

thorax may involve difficulty breathing. Radiation is considered a local, rather than systemic treatment, in which high-energy beams are aimed at cancer cells with the goal of damaging their DNA in the cancerous cells, such that they may fail to reproduce and ultimately die. The side effects of radiation therapy may build up over time, and may include pain,[45] but are generally considered more treatable and tractable than those adverse effects associated with chemotherapy. Chemotherapy is a systemic treatment aimed at destroying or slowing cancer cell growth. Side effects can have a severe negative impact on quality of life, sometimes causing anemia, anorexia, fatigue, nausea and vomiting, esophagitis, neutropenia, myelosuppression, and thrombocytopenia. These conditions can translate to weakening of the immune system, anorexia, bleeding, irritation, or inflammation. Some chemotherapies (e.g. vincristine) cause pain by direct toxicity to nerves; peripheral neuropathy is an important painful chemotherapy sequalea. Chronic pain may be experienced when patients are immobile, or when they try to eat or conduct normal daily activities (source: NCI). Pain associated with chemotherapy may be severe and debilitating, and the association between chemotherapy and pain is strong and well-established. However, it is important to acknowledge also that as it succeeds in shrinking tumors and alleviating disease-related symptoms including pain, chemotherapy may also have palliative effects.[46]

Hormonal therapy for women has historically consisted of tamoxifen and other anti-estrogen agents, and is associated with side effects similar to the symptoms of menopause, including hot flashes, irregular menstrual periods and vaginal discharge or bleeding. Hormonal therapies have the potential to reduce pain, but quality of life issues are of greater interest than pain when evaluating the effects of hormonal treatment. New classes of hormonal therapies called anti-aromatase agents are emerging as an important class of

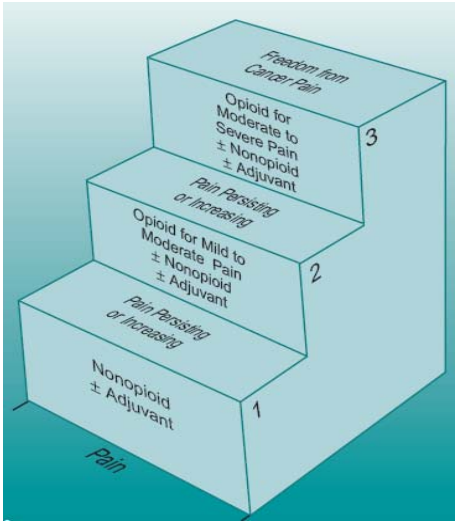
hormonal agents to treat breast cancer; thus far, pain has not emerged as a major side effect of these therapies. It is important to note that if hormonal or other therapies create sleep disturbances, patients' resilience/resistance to pain may be impaired by sleep deprivation.

Therapeutic interventions for cancer pain

Cancer pain can be alleviated when any of the interventions described above to treat the disease are successful. In addition, radiation, chemotherapy, surgery (as in creation of nerve blocks to prevent pain), or pharmacologic agents may each be administered solely for palliative purposes. Analgesics used to treat cancer pain fall into three main categories: (1) non-steroidal anti-inflammatory agents (NSAIDs) or acetaminophen, (2) opioids, and (3) adjuvant analgesics, which may treat concurrent pain-exacerbating symptoms such as insomnia or vomiting, enhance the analgesic efficacy of opioids, or provide analgesia for specific types of pain. Adjuvant analgesics include antidepressants, anticonvulsants, corticosteroids, laxatives, and antiemetics (among others). Drugs from the three families of analgesics are often given in combination.[47] Cyclooxygenase-2 (COX-2) inhibitors, a class of NSAID was introduced in 1999, but COX-2 inhibitors are now less widely available in the U.S. following their market recall in 2004 related to risk of heart attack and stroke. In prescribing it may be useful to categorize pharmacologic analgesics based on their drug-metabolizing enzymes (DMEs), and then use information about cytochrome p450 (CYP) genotypes to improve chances of successful pain treatment. In addition to pharmacological agents, non-pharmacological modalities are commonly used as adjuvants. The non-pharmacological modality may be general (e.g. visual imagery) or pain-etiology specific (e.g. acupuncture, ice).

Figure 4.Analgesic ladder for treatment of cancer pain. World Health Organization (reproduced with permission).

Figure 4 depicts a widely known modular approach to management of cancer pain, developed by the WHO, referred to as the "three-step analgesic ladder" (or "staircase"), from: Cancer pain relief and palliative care. Report of a WHO expert committee (WHO Technical Report Series, 804.1-75. 1990. Geneva, World Health Organization). The first tier, for mild to moderate pain, consists of NSAIDs and acetaminophen with or without adjuvant interventions. As pain escalates or persists, treatment progresses to the second tier, in which an opioid, such as codeine, hydrocodone or low-dose morphine, is added to the NSAID with or without an adjuvant intervention.[47] If pain persists beyond step 2, pain treatment progresses to the third tier where treatment consists of stronger opioids such as higher-dose morphine, hydromorphone, methadone, fentanyl, or oxycodone (all known as full opioid agonists). The WHO analgesic ladder approach to managing cancer pain has been criticized for emphasizing by-the-clock rather than as-needed dosing and careful therapy individualized to each patient.[47] Although the WHO analgesic ladder is widely known and used, validation studies of its efficacy (i.e., studies designed to gain information on reliability over time of the measure's ability to consistently manage pain successfully) are limited,[48,49] and pain researchers and practitioners continually debate the appropriateness of its structure and application. The WHO pain ladder is a treatment guideline that involves the tiered categorization of pain as mild, moderate, or severe. Although the WHO ladder does not demarcate specific cutoffs on a pain NRS,



implementation of guidelines that rely on such tiered categorizations rely also on the findings of studies that establish numeric cutpoints on numeric pain rating scales to distinguish mild, moderate, or severe pain on the scale.[9] The application of the WHO ladder tool to NRSs for the purpose of treatment decisions is considered a modular pain management strategy.

The WHO has also made recommendations that focus on forming a more effective policy of pain control throughout the world. These recommendations consider the shift toward symptom palliation and increasing survival than toward curing the cancer. Because changes in pain can be important signals of disease progression that call for adjustments in intervention, treatment strategies that use signs other than pain to evaluate disease progression are important in ensuring that pain treatment does not decrease treatment effectiveness.

ECOG performance status and disease progression have been found to be two important indicators of cancer severity.[50-53] For the present study, ECOG performance status is considered as a baseline covariate in Manuscript 1, and a time-dependent covariate in Manuscript 2.

Racial disparities in cancer and cancer pain

In past research, racial/ethnic minority status has been found to be of consistent value in predicting worse outcomes; a review of the literature on disparities in breast cancer found that African-American women are at higher risk for breast cancer mortality than their white counterparts.[54] With regards to disease severity and mortality, a recent study of survival in the Carolina Breast Cancer Study found that African-American women were genetically at higher risk than Caucasian women for a faster-progressing basal form of breast cancer.[55] This finding could mean greater potential for pain risks due to faster disease progression among

African-American women with breast cancer. Across diseases and settings, white and socially privileged patients appear to receive far better pain management than ethnic and social minorities.[8] One study concludes that ethnicity is a factor contributing to inadequate pain assessment and treatment, with patients of color reporting more pain than Caucasians.[56] This finding was corroborated by another study that found that African-American patients (a) reported more daily pain (34% as compared to 25% of white patients), (b) had greater odds of failing to receive any analgesic agent, and (c) were found to have inadequate pain management at higher rates than white patients in outpatient clinics.[57] Such disparities have been further confirmed and discussed in other investigations, which have cited differences in treatment patterns, pain management strategies, and the use of hospice care as potential contributing factors.[54,58,59] Further study is recommended on patient- and physician-level factors in pain disparities.[56]

To improve both disease and pain outcomes, we must address the sources of the disparities that have been so consistently observed and documented in pain research. The sources of pain disparities by minority status are complex, simultaneously involving factors on all levels of health and health care. The present study aims to improve our understanding of risk factors for pain experienced over time, further examining race as a risk factor by investigating the hypothesis that pain over time is experienced differently between Caucasian and non-Caucasian patients with metastatic disease.

Bisphosphonates and pain

The data for the present study come from a bisphosphonate clinical trial. Bisphosphonates are a class of drugs that include clodronate, ibandronate, pamidronate, and zoledronate. They are commonly used as an adjuvant pain treatment using the WHO cancer

pain analgesic ladder. According to one review of the role of bisphosphonates in treatment of bone metastases, pamidronate is recommended in women with pain caused by osteolytic metastasis to relieve pain when used concurrently with systemic chemotherapy and/or hormonal therapy, since the authors found that pamidronate treatment was associated with a modest pain control benefit in clinical trials included in the review.[60] The reviewers' conclusions from a 2004 Cochrane review of bisphosphonates for relief of bone pain secondary to metastases state that: "There is evidence to support the effectiveness of bisphosphonates in providing some pain relief for bone metastases… [but] there is insufficient evidence to recommend bisphosphonates for immediate effect; as first line therapy; to define the most effective bisphosphonates or their relative effectiveness for different primary neoplasms. Bisphosphonates should be considered where analgesics and/or radiotherapy are inadequate for the management of painful bone metastases." [61] Another 2005 Cochrane review concluded that bisphosphonates reduce skeletal events and bone pain in advanced breast cancer where bone metastasis is present.[62] It is useful in interpreting the findings of the present study to keep in mind that all of the patients under study (i.e., both treatment arms) were being treated with bisphosphonates and adjuvant standard therapy. Substantive differences in analgesic effects comparing specific bisphosphonates have not as yet been established, but the effect of bisphosphonate treatment on the present study sample is potential underestimation of pain.

C. Literature search strategies

Pain in cancer is a popular topic of scientific inquiry, leading to a particularly large body of existing and growing literature on the subject. The advantage of a vast body of relevant literature is that in undertaking a new study, one has available numerous multi-faceted and

varied sources of information virtually limitless in depth and scope. However, while in the case of a small existing body of research, one could feasibly read at least the abstracts of everything that had been published on the topic and then select the most relevant works from among that comprehensive set of initial search results; comprehensive review is more of a challenge with a large body of literature. A careful strategy must be implemented to select those works as candidates for closer examination.

The reference seeking strategy was implemented at every stage of the research, up to the point of final acceptance of each resultant manuscript for publication. The strategy involved a combination of (a) database searching, (b) priority to syntheses and critical assessments that have resulted from systematic evidence reviews already conducted to date, (c) advice from cancer pain experts on identifying key studies, (d) previous relevant work that members of the committee and I have conducted in collaboration with other researchers, (e) Institute for Scientific Information (ISI) Web of Science citation links, (f) mining of existing reference lists, and (g) using the internet through Google Scholar searches or organization web pages (e.g., American Pain Society). All references must have been listed in PubMed or another UNC Health Sciences Library electronic database, or retrieved from government or society websites (in the case of reports) in order to be included in the present literature review.

A search was conducted of the MEDLINE database through PubMed (1957 to present, U.S. National Library of Medicine). Medical Subject Heading (MeSH) terms were used when searching this database wherever possible. The first search was as follows: ("Pain"[MeSH] OR "Pain, Intractable"[MeSH] OR "Pain Measurement"[MeSH]) AND "Neoplasms"[MeSH]). This search came up with 17,427 records. When these results are limited to English and Human studies, 12,936 records result. Table 1 shows how this set of

results served as the root for the concept of "cancer pain", and then was combined using the Boolean operator "and" with other concepts of interest, such as longitudinal study and pain management (including treatment guidelines and algorithms) to narrow search results. Roots for key concepts are indicated in italics.

Table 1. Pubmed literature search narrowing strategy

Search #	Goal	Query	Results
	CANCER PAIN		
#1	Cancer Pain	Search ("Pain"[MeSH] OR "Pain, Intractable"[MeSH] OR "Pain Measurement"[MeSH]) AND "Neoplasms"[MeSH]	17,427
#2	*Root for Cancer Pain*	Search ("Pain"[MeSH] OR "Pain, Intractable"[MeSH] OR "Pain Measurement"[MeSH]) AND "Neoplasms"[MeSH] Limits: English, Humans	12,936
	LONGITUDINAL		
#3	"Longitudinal Studies" (MeSH)	Search "longitudinal" Limits: English, Humans	405,974
#4	"Repeated measures" (Non-MeSH)	Search "repeated measures" Limits: English, Humans	6,511
#5	*Root for Longitudinal*	Search #3 OR #4	411,152
#6	Cancer Pain - longitudinal	Search #2 AND #5	1,327

The search narrowing strategy then involved reviewing the titles and abstracts among sets of references retrieved through PubMed for relevance and potential contribution to the present study. Those works deemed through this qualitative process to be of greatest relevance and timeliness were selected for inclusion in the critical review of the literature.

D. Critical review of literature

Critical assessment of the literature relies in part upon evidence grading systems such as that described by Sackett and colleagues to rank methodological rigor.[63] In evaluating the literature, I employed the method used by Jadad and colleagues in their 1995 study exploring the evidence for the WHO analgesic ladder.[49] This method is described in the Ontario Cancer Treatment Practice Guidelines,[64,65] and is modified from Sackett (1989)[63] and Cook (1992).[66] It is important to note that evidence grading systems are limited for assessing quality of observational studies. Critical assessment has relied also upon the inclusion and exclusion criteria used in existing systematic evidence reviews, as well as expert opinion. My ability to qualitatively assess the relevance of different works is informed by my past research experience and tools for evaluating methodology and study design. Publications on which I have collaborated as an author include (a) an NCI-funded study of patient decision making in advanced-stage cancer,[15] (b) a study of patient characteristics relating to expectations of benefit from phase I trials,[16] (c) how conceptions of risk among patients with advanced cancer play into their treatment choices,[67] (d) an economic study comparing two bisphosphonate treatments as part of palliative care in outpatient settings in the U.S.,[68] and (e) the subsequent adaptation of this economic model to the Canadian palliative care setting.[69]

Syntheses of large sets of articles published on cancer pain have been conducted in the form of evidence-based reports; these large-scale reviews offer some distinct advantages. First, these reports are compiled by initially casting a wide net in gathering virtually all relevant peer-reviewed literature published on the topic within a given timeframe, ensuring a comprehensive collection of literature from which the reviews are drawn. Next, by applying methodological criteria to assess the design and relevance of the studies gathered, greater weight in the synthesis is given to those studies of higher methodological rigor and scientific value. Lastly, through their synthesis of the most relevant background issues (studies of prevalence, measurement and interpretation, and pain-related effects of treatments and analgesics), such reports often provide a considered assessment of the present state of knowledge, identifying where gaps in current knowledge exist. Table 2 shows the list of key publications selected for evidence extraction. Figures 5-17 are evidence extractions for the most recent of these works. The evidence extraction follows the template used for AHRQ evidence reports, and focuses on study-specific methods, findings, and limitations for each study.

Table 2. Literature chosen for evidence extraction/review.

Article #	Title and First Author, if listed	Agency (if report) Citation (if article)	Year	Figure #
1	Bisphosphonates for breast cancer (Review). Pavlakis N	Cochrane Reviews	2006	5
2	Ethnic Differences in Pain Among Outpatients with Terminal and End-Stage Chronic Illness. Rabow MW, Dibble SL.	Pain Medicine; 6:235-241	2005	6
3	American pain society recommendations for improving the quality of acute and cancer pain management. Gordon D.	Arch Intern Med. 2005 Jul 25;165(14):1574-80.	2005	7
4	Categorizing the severity of cancer pain: further exploration of the establishment of cutpoints. Paul SM.	Pain 2005; 113:37-44	2005	8
5	Occurrence of cancer pain. McGuire DB.	J Natl Cancer Inst Monogr: 51-56	2004	9
6	Bisphosphonates for the relief of pain secondary to bone metastases. Wong R.	Cochrane Reviews	2004	10
7	A clinical decision and economic analysis model of cancer pain management. Abernethy AP.	Am J Manag Care; 9:651-664	2003	11

Article #	Title and First Author, if listed	Agency (if report) Citation (if article)	Year	Figure #
8	The Unequal Burden of Pain: Confronting Racial and Ethnic Disparities in Pain. Green CR	Pain Medicine; 4:277-294	2003	12
9	Management of Cancer Symptoms: Pain, Depression, and Fatigue. Carr D.	AHRQ	2002	13
10	Management of cancer pain. Evidence Report/Technology Assessment No. 35. Goudas L.	AHRQ	2001	14
11	Implementing Guidelines for Cancer Pain Management: Results of a Randomized Controlled Clinical Trial. DuPen S.	J Clin Oncol. Jan 1999;17(1):361-370.	1999	15
12*	The management of chronic pain in patients with breast cancer. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer.	Canadian Society of Palliative Care Physicians. Canadian Association of Radiation Oncologists	1998	A
13	The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. Jadad A.	JAMA. Dec 20 1995;274(23):1870-1873.	1995	16

Article #	Title and First Author, if listed	Agency (if report) Citation (if article)	Year	Figure #
14	When is cancer pain mild, moderate or severe? Grading pain intensity by its interference with function. Serlin RC.	Pain 1995; 61:277-284	1995	17
15*	Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1. Jacox A.	AHRQ (AHCPR at time of publication)	1992	[A]

[A] Indicates a reference not included in the review because it is an outdated guideline. Using survival analysis techniques, Shekelle and colleagues estimate that clinical practice guidelines become outdated after about 6 years. To ensure the timeliness of information in this critical literature review, only works of particular relevance that are older than 7 years as of 2006 are included in the evidence extraction phase.

Figure 5. Evidence extraction: Pavlakis N, et al. 2005.

Title, Citation, and Authors	Year	Design	Methods	Findings	Conclusions and Limitations
Bisphosphonates for breast cancer. Pavlakis, N., R. Shmidt et al. Cochrane Database Syst Rev (3) : CD 003474	2005	Assessment of effects of bisphosphonates on skeletal events, bone pain, quality of life and survival in women w/ early and advanced breast cancer. Study Reviewed 21 Randomized Controlled Trials Selected by two independent reviewers.	Meta-Analyses were based on the fixed-effects model (Mantel-Haenszel).	Statistically significant effects of several bisphosphonates, were found (both oral and iv) in women with advanced breast cancer and evident bone metastases. 7 studies showed improvement in bone pain in these women. 3 studies showed Ibandronate (oral & iv) as improving global quality of life.	Good results in reduction of skeletal event, and bone pain for advanced breast cancer + bone metastases. No significant evidence w/o bone metastases even for advanced breast cancer. No results on optimal timing of initiation of therapy and treatment duration.

Figure 6. Evidence extraction: Rabow MW and Dibble SL, 2005.

Title, Citation, and Authors	Year	Design	Methods	Findings	Conclusions and Limitations
The unequal burden of pain: disparities and differences(continuation) Ethnic differences among outpatients with terminal and end-stage chronic illness Rabow MW and Dibble SL	2005	To explore ethnic and country of origin differences in pain among outpatients with terminal and end-stage chronic illness. Cohort study within a year-long trial of palliative care consultation. Setting: Outpatient general medicine practice in an academic medical center. 90 patients with advanced congestive heart failure, chronic obstructive pulmonary disease, or cancer, and with a prognosis between 1 and 5 years.	Outcome measures. Patients' report of pain using the Brief Pain Inventory and analgesic medications prescribed by primary care physicians. Differences in pain report and treatment were assessed at study entry, at 6 and 12 months.	The overall burden of pain was high. White patients reported less pain than others (in least, average and current pain). No significant differences were found between Asian, Black, and Latinos patients. No differences between US born patients and others.	No differences in pain in regard to country of origin, or minority ethnicities, but difference between white and non-white. Patients of all ethnicities are inadequately treated for their pain, and further study is needed to determine the relative patient and physician contributions to the finding of unequal symptom burden and inadequate treatment effort.

Figure 7. Evidence extraction: Gordon D, et al. 2005.

Title, Citation, and Authors	Year	Design	Methods	Findings	Conclusions and Limitations
American Pain Society Recommendations for Improving the Quality of Acute and Cancer Pain Management. Debra B. Gordon et al. – APS Quality of Care Taskforce. Archives of Internal Medicine / Vol 165	2005	1995 APS Quality Improvement Guidelines for the Treatment of Acute Pain and Cancer Pain were revised. Study Review Based on 51 articles from Medline & Cumulative Index to Nursing & Allied Health Databases, from 1994 through may 2004.	Reviews by 11 multidisciplinary members of APS with expertise in Quality Improvement or Measurement. 5 experts from organizations that focus on health care quality reviewed final recommendations. 3000 members of APS were invited to provide input.	Assessment and communication are not sufficient to improve quality of pain management. Implementation and improvements in pain treatment that are timely, safe, evidence based and multimodal are needed.	Updated and expanded Guidelines with new Quality Indicators and measures. Recommendations focus on Acute Pain and Cancer Pain, because of a lack of evidence & consensus about assessment and treatment of chronic non cancer pain.

Figure 8. Evidence extraction: Paul SM, et al. 2005.

Title, Citation, and Authors	Year	Design	Methods	Findings	Conclusions and Limitations
Categorizing the severity of cancer pain: further exploration of the establishment of cutpoints. Pain; 113:37-44 Paul SM, Zelman DC, Smith M, et al.	2005	Purposes: to determine the optimal cutpoints for mild, moderate, and severe pain based on patients' ratings of average and worst pain severity, using a larger range of potential cutpoints, and to determine if those cutpoints distinguished among the three pain severity groups on several outcome measures. Secondary analysis of 212 oncology patients	ANOVA and MANOVA to establish cutpoints, with F test statistic	Results confirm a non-linear relationship btw. cancer pain severity and interference and also confirm that the boundary between a mild and a moderate level of cancer pain is at 4 on a 0-10 numeric rating scale. However, results did not confirm Serlin severe cutpoint of 7. This study found ≥ 7 to be severe.	Present study was a homogenous pt. population, not multinational like Serlin. Serlin pts. Were recruited both inpatient and outpatient Settings. Concludes that there is a need for further exploration of pain cutoffs for severity.

Figure 9. Evidence extraction: McGuire DB, 2004.

Title, Citation, and Authors	Year	Design	Methods	Findings	Conclusions and Limitations
Occurrence of Cancer Pain. Deborah B. McGuire Journal of the National Cancer Institute Monographs No. 32	2004	Defines the limitations and inadequacies of pain related studies. Makes recommendations for design and methods of pain studies. 43 studies were reviewed.	Critical review; monograph	Researchers have inadequately studied pain, using small, heterogeneous samples, with undifferentiated causes in a cross sectional format, yielding little to no usable data.	Studies need to focus on homogeneous classification, longitudinal approach across all phases of trajectory, homogeneous samples (population groups, types of cancer, types of pain).

Figure 10. Evidence extraction: Wong R and Wiffen PJ, 2002.

Title, Citation, and Authors	Year	Design	Methods	Findings	Conclusions and Limitations
Bisphosphonates for the relief of pain secondary to bone metastases. The Cochrane Database of Systematic Reviews 2002, issue 2. Art. No: CD002068 Wong R, Wiffen PJ	2002	To determine the effectiveness of bisphosphonates for the relief of pain from bone metastases. Review of Randomized trials where pain and/or analgesic consumption were outcome measures. 30 studies used (21 blind, 4 open, 5 active control). Total of 3682 patients.	Proportions of patients with pain relief at 4, 8 and 12 weeks were assessed.	8 studies showed NNT at 4 weeks of 11, and at 12 weeks of 7. 1 Study showed a small improvement in quality of life at 4 weeks.	There is evidence to support the effectiveness of bisphosphonates in providing some pain relief for bone metastases. Insufficient evidence to recommend as first line therapy. Bisphosphonates should be considered where pain persists through analgesic and /or radiotherapy.

Figure 11. Evidence extraction: Abernethy AP, et al. 2003.

Title, Citation, and Authors	Year	Design	Methods	Findings	Conclusions and Limitations
A clinical Decision and Economic Analysis Model of Cancer Pain Management. The American Journal of Managed Care, Vol. 9, No.10. Amy P. Abernethy Gregory P. Samsa, David B. Matchar	2003	Designing model that educates clinical decision makers and healthcare professionals about cancer pain and effectiveness of pain management strategies. Tailored cost-effectiveness analysis using an evidence based decision analytic model.	Model compares: - Guideline-Based Care (GBC) - Oncology-Based Care (OBC) - Usual Care (UC) Model calculates likelihood of cancer pain in population, pain management effectiveness, and cost of pain management.	After one month, percentage of patients with effective pain management and cost per type of care: GBC: 80%- $579 OBC: 55%- $466 UC: 30% - $315	Guideline based Cancer Pain Management leads to improved pain control with modest increases in resource use.

Figure 12. Evidence extraction: Green CR, et al. 2003.

Title, Citation, and Authors	Year	Design	Methods	Findings	Conclusions and Limitations
The unequal burden of pain: confronting racial and ethnic disparities in pain. Green DR et al.[8]	2003	To provide pertinent evidence regarding differences in pain perception, assessment and treatment for racial and ethnic minorities.	Review article – Selective literature review performed by experts in pain.	Racial and ethnic disparities in pain perception, assessment and treatment were found in all settings, and across all types of pain. The literature suggests that the sources of disparities are complex and involve patients, health care provider, and health care system.	There is a need for a comprehensive pain research agenda with improved training for health care providers and educational interventions for patients.

Figure 13. Evidence extraction: Carr D, et al. 2002.

Title, Citation, and Authors	Year	Design	Methods	Findings	Conclusions and Limitations
Management of Cancer Symptoms: Pain, Depression, and Fatigue. Evidence Report/Technology Assessment No. 61 AHRQ Publication No. 02-E032. Rockville, MD: Agency for Healthcare Research and Quality. Carr D, Goudas L, Lawrence D, et al.	2002	Evidence report on the topic of Management of Cancer Symptoms: Pain, Depression, and Fatigue was produced on request from the Office of Medical Applications Research, National Institutes of Health, and the National Cancer Institute for a Consensus Developmental Conference. The purpose was to review available evidence on cancer symptom management.	English, 1966 - September 2001 in mainly MEDLINE, CANCERLIT, Cochrane. > 200 English-language articles. Specific inclusion criteria and methods of synthesis were developed for each of the topics. Relevant data were abstracted and synthesized.	Prevalence of cancer pain varied from 14 to 100%, dependent on setting. More than 100 scales used to assess pain. Randomized controlled trials (RCTs) establish that many current treatment modalities can individually reduce cancer pain. For specific problems such as postherpetic neuralgia and oral mucositis, there are sufficient trials upon which to base specific treatment recommendations	Pain, depression, and fatigue are common problems among patients with cancer. Few high-quality RCTs to help guide treatment decisions. Additional studies are needed on prevalence and impact of these symptoms, and to define factors that correlate with these symptoms. Paucity of studies in children.

Figure 14. Evidence extraction: Goudas L, 2001.

Title, Citation, and Authors	Year	Design	Methods	Findings	Conclusions and Limitations
Management of cancer pain. Evidence Report/Technology Assessment No. 35 AHRQ Publication No. 02-E002. Rockville, MD: Agency for Healthcare Research and Quality. Goudas L Carr D, Bloch R, et al.	2001	Report summarizes published evidence on the prevalence of cancer-related pain and the efficacy of drug and nondrug therapies for its treatment.	English, human – mainly Medline, CancerLit, and the Cochrane Controlled Trials Registry (1966 to December 1998). Searched approximately 19,000 titles and identified 22 epidemiologic surveys, 188 randomized controlled trials, and 100 nonrandomized studies of treatments of cancer-related pain. Meta-analysis was performed when there were sufficient data to address a specific question.	Cancer pain adds substantially to the already considerable national disease burden of cancer, particularly in minorities, women, and the elderly. Survey data for the most part do not track pain and other symptoms longitudinally across time. Epidemiological data indicate cancer pain relief may be inadequate.	Need for developmentally appropriate and culturally sensitive pain assessment instruments that are reliable and easy to administer. The growth in sophistication of quality-of-life assessment and advances in the field of chronic pain treatment that model relationships between pain, disability, and impairment offer a valuable opportunity to understand these interactions in the context of cancer pain

Figure 15. Evidence extraction: DuPen SL, et al. 1999.

Title, Citation, and Authors	Year	Design	Methods	Findings	Conclusions and Limitations
Implementing Guidelines for Cancer Pain Management: Results of a Randomized Controlled Clinical Trial. DuPen SL et al. Journal of Clinical Oncology, 17 (1): 361-370[71]	1999	Clinical guidelines for cancer pain mgmt. were implemented and evaluated in the community setting for whether they improved care. Prospective randomized longitudinal controlled study. 81 cancer pts. aged 37 to 76 yrs.	Relied on Cleeland pain treatment algorithm and AHCPR guidelines. 3-month study with periodic assessment of outcomes: BPI, Pain Treatment Acceptability Scale, Side effects, and FACT.	Patients Randomized to algorithm group achieved statistically significant reduction in usual pain intensity. Concurrent chemotherapy and patient adherence were significant mediators of worst pain. No significant difference in quality of life or other symptoms between groups.	Study supports use of algorithmic decision making in cancer pain mgmt. Comprehensive pain assessment and evidence-based processes enhance usual pain outcomes. Small sample size; worst pain may be constant or breakthrough

Figure 16. Evidence extraction: Jadad AR and Browman GP, 1995.

Title, Citation, and Authors	Year	Design	Methods	Findings	Conclusions and Limitations
The WHO Analgesic Ladder for Cancer Pain Management. Stepping Up the Quality of Its Evaluation. Jadad AR and Browman GP JAMA, Vol 274, No. 23.	1995	Systematic review of studies evaluating the effectiveness of the World Health Organization analgesic ladder as an intervention for cancer pain management. studies from various sources (MEDLINE 1982 to 1995, textbooks, reference lists)	8 studies purporting to evaluate the effectiveness of the WHO ladder were included in the review.	69% to 100% of patients achieved adequate analgesia. Studies did not provide information on pain assessment, were retrospective, had high withdrawal rates, or short follow up periods etc. No other conclusions could be reached.	Studies provide some valuable information on the course of cancer pain and its treatment. However the evidence they provide is insufficient to estimate confidently the effectiveness of the WHO analgesic ladder for cancer pain treatment.

Figure 17. Evidence extraction: Serlin RC, et al. 1995.

Title, Citation, and Authors	Year	Design	Methods	Findings	Conclusions and Limitations
When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain; 61:277-284 Serlin RC, Mendoza TR, Nakamura Y, et al.	1995	Purpose was to determine at what points we can best distinguish "mild" from "moderate" from "severe" pain on the BPI. N = 1897 pts. w metastatic cancer and pain. 4 samples in US, France, China, and Philippines.	ANOVA and MANOVA analyses with F test statistic	Found optimal cutpoints that form 3 distinct levels of pain severity on 0-10 NRS. 1-4: mild, 5-6: moderate, 7-10: severe. Also found non-linear relationship between the BPI severity and interference scales.	The analysis established useful severity cutpoints using a diverse sample. The 3-tiered metric is especially relevant to the WHO analgesic ladder.

In compiling, evaluating, interpreting, and synthesizing results from many relevant epidemiological studies, especially those reporting results of cancer pain clinical trials, the Agency for Healthcare Research and Quality (AHRQ) has created two evidence-based reports (summarized in Figures 13 and 14 above) of particular use in establishing the present state of knowledge about cancer pain. The first of these two reports was published in 2001, entitled *Management of Cancer Pain*.[47] One of the main objectives was to summarize published evidence on the prevalence of pain related to cancer; cancer-related pain was defined as pain caused by cancer, by cancer treatment such as surgery, radiation, or chemotherapy, or by the side effects of treatment. The authors found that cancer's impact on public health is due to its considerable prevalence in the world and its association with devastating morbidity and mortality,[72-74] and that pain is a key dimension of the degradation of quality of life associated with this disease.[1,2] The report reviewed observational studies on the epidemiology of cancer pain, randomized controlled trials, and selected nonrandomized studies. Their search strategy was unrestricted by age, gender, ethnicity, or type of cancer, and excluded studies of acute postoperative pain. The method used to ascertain studies for review in the 2001 report was to identify English language human studies by searching Medline, CancerLit, and the Cochrane Controlled Trials Registry, published from 1966 to December 1998. These search results were supplemented by bibliographies and other sources, yielding approximately 19,000 titles. The authors then narrowed this list using a multidimensional evidence grading scale that evaluated validity, quality, and relevance.

Ultimately, the 2001 report summarized 24 epidemiological surveys of cancer pain[7,30,57,75-96] and abstracted results from 188 randomized controlled trials of cancer pain treatment into evidence tables. Each trial was assessed according to its methodological

quality and applicability. Meta-analysis was performed when there were sufficient data to address a specific question. The report also examined data from 100 nonrandomized studies. The median number of patients enrolled in the randomized trials of primary analgesics (NSAIDs, opioids, and adjuvants) was found to be 70 or fewer. Information about the location, nature, and mechanism of pain before and after treatment was minimal for all interventions examined. Heterogeneous reporting of outcomes, nonuniformity of pain measurements, and incomplete reporting of relevant data precluded all but three meta-analyses. The report concludes that randomized controlled trials have established many current treatment modalities effective in individually reducing cancer pain. However, these trials constitute only a hundredth of the published literature on cancer pain, enroll only 1 in 10,000 patients at risk for cancer pain in developed countries, are often heterogeneous, and are often of poor methodological quality, leaving several questions unanswered that the report originally set out to investigate, such as: "what are the epidemiological characteristics of cancer-related pain, including pain caused by cancer, by procedures used to treat cancer, and by the side effects of cancer treatment?", and "What is the relative efficacy of current analgesics for cancer pain?".[47] Studies of risk factors suggest that age, gender, tumor type, genetics, psychosocial context, and culture affected pain and analgesic efficacy. This particular report concludes that more research, especially in the form of higher-quality clinical trials, will be needed to advance progress in cancer pain relief. Other studies of risk factors for pain have found that among patients with breast cancer, younger patients are at higher risk for post-treatment pain.[45,97] Minority patients have been found consistently to be at greater risk of worse pain outcomes and of undertreated cancer pain specifically.[8,24,25,56] Recent studies (in addition to the evidence-based reviews discussed) have cited the need for

future studies to identify specific risk factors and investigate those risk factors identified to date.[6,98]

In 2002 the AHRQ released a followup to its 2001 report entitled *Management of Cancer Symptoms: Pain, Depression, and Fatigue*[5]. The 2002 report identified and summarized the findings of 29 epidemiological studies, including the 24 studies reviewed in the first report plus five additional studies[99-103] identified between 1998 and 2001. Several studies reported on the prevalence and/or incidence of cancer-related pain. These were nationwide or multicenter surveys including as many as 35,000 patients, and hospital or clinic-based surveys including a few hundred or fewer patients. More than half of the studies were conducted in the United States. The majority of the remaining studies were from Europe. No single survey identified a pain prevalence rate below 14% of the patients surveyed. Disease severity was found to be associated with more pain, and analgesics were found to be sometimes (but not always) successful in alleviating pain. Other than these two evident themes, there were no other clear associations, consistent across studies, between the prevalence or incidence of pain and specific patient factors, disease characteristics, the setting in which care is provided (e.g., primary care or specialized oncology or pain treatment clinics), or specific treatments directed towards the underlying disease. The report makes several other conclusions; first, they note that findings from observational and survey studies indicate that the majority of patients with cancer experience pain at some point during their treatment, and that cancer pain impairs both patients' quality of life and functional status. The report states that the further along disease has progressed, the greater the likelihood of pain and severe pain. It is important to note that the timeline for progression varies by patient

and tumor type. Thus, disease progression is preferable to time for use as an indicator of potentially increasing pain.

The authors of the same 2002 report[5] identified evidence indicating that undertreated pain adds substantially to the disease burden imposed by cancer, and that despite advances in treatment, the disease continues to cause great suffering both among those who die and among those who survive. Pain is often not eliminated, even when standard analgesic therapy practice is implemented according to the WHO ladder method for treating cancer pain. The current literature does not yet provide a comprehensive description of the patient's experience of pain over the course of treatment or continuum of care. The report cites a need for tumor-specific studies of longitudinal pain trajectories, with consideration of how various treatments available might affect patients' experience of pain during their treatment.

The 2004 monograph by McGuire[6] summarized in Figure 9 is particularly critical of existing cancer pain studies in terms of epidemiological and methodological quality. The author concludes from the review that there is a need for tumor-specific information on patients' experiences of pain over time.

Study of disparities in pain outcomes by racial and ethnic minority status has evolved within the fields of research on both pain in general as well as cancer pain specifically. A 2003 review by Green and colleagues (Figure 12) summarizes findings of studies to date on pain disparities (across diseases and settings), focusing on differences in quality of care between non-minority and minority patients. Several areas of the issue are examined. In the area of experimental pain research, Campbell and colleagues observed that non-Caucasians appeared to have lower pain thresholds and tolerance than Caucasians when tested for electrical, heat, pressure and cold pressor pain.[104] African-Americans in that study reported

greater use of passive pain coping strategies and more hypervigilance. However, controlling for these factors still did not eliminate the differences in pain responses by race.[104] In the area of communication, better patient-physician communication was reported in racial/ethnic concordant patient-physician pairs, along with higher patient involvement in medical decisions. The authors state that pain assessment is inadequate as soon as pain is reported as severe, and that minorities are consistently undertreated, with ethnicity and gender influencing physician management. On the system level, findings are reported that suggest disparities. For example, insufficient quantities of opioid analgesic were found in stock in pharmacies associated with higher minority population areas in New York City. From their comprehensive review, the authors conclude that white and socially privileged patients receive far better pain management than ethnic and social minorities.[8]

Rabow and Dibble (2005) sought to examine not only the influence of ethnic and geographical factors on specific disease-related pain, but also which deficiencies in end-of-life care are involved in the inadequacy of pain treatment. The findings summarized in Figure 6 indicate that ethnicity is a factor contributing to inadequate pain assessment and treatment, with patients of color reporting more pain than white Caucasians. The authors attribute their findings to a previously well-documented and established pattern of both physicians inattention to their patients' pain and physicians' resistance to the advice of specialist consultants.[56]

In a 2003 evaluation by Abernethy and colleagues[105] of a pain treatment decision analytic model (Figure 11), the authors compared three pain management strategies using an adaptable spreadsheet model with inputs from published U.S. population demographics, cancer registry data, high-quality studies of cancer pain management, standard

reimbursement schedules, and expert opinion. The three strategies compared were (1) guideline-based care, (2) oncology-based care, and (3) usual care. Outcomes calculated included the likelihood of cancer pain in a healthcare population, how effectively that pain is managed, and average monthly cost of treatment. This study concluded that cancer pain management based on guideline-based care led to improved pain control, with modest increases in resource use.

The 1999 study by Du Pen and colleagues (Figure 15) is of particular importance in synthesizing information about guideline effectiveness.[71] Patients were randomized to receive either (1) standard-practice pain and symptom management therapies used by community oncologists, or (2) pain management care according to an algorithm derived from the AHCPR (now AHRQ) guidelines discussed above.[5] Patients randomized to the algorithm group achieved statistically significant reductions in usual pain intensity. Concurrent chemotherapy and patient adherence were found to be significant mediators of worst pain. No significant differences in quality of life or other symptoms were observed between groups. The Du Pen study supports the use of algorithmic decision making in accordance with current guidelines for cancer pain management The authors conclude that comprehensive pain assessment and evidence-based processes enhance usual pain outcomes.[71]

A few studies have further developed the BPI measure by classifying pain into severity categories according to cutpoints on a 0-10 numeric rating scale. This classification is of extensive use in research and clinical practice. Cutpoints are used to drive treatment decisions, develop practice guidelines, and determine effectiveness of interventions. Where the cutoff point is set for severe pain also affects descriptive epidemiology, including

etiological reports on longitudinal cancer pain, as well as prevalence estimates at a given time point.[9-12] The Serlin study (Figure 17), conducted among metastatic cancer patients, found optimal cutpoints that form 3 distinct levels of pain severity on 0-10 NRS. 1-4: mild, 5-6: moderate, 7-10: severe. Serlin and colleagues also found non-linear relationship between the BPI severity and interference scales. The findings of a 2005 study by Paul and colleagues[10] in outpatient oncology patients with metastases confirmed Serlin and colleagues' finding of a non-linear relationship between cancer pain severity and interference. However, the Paul study (see Figure 8) found a slight difference regarding the severity cutpoint of 7. While the Serlin classification would categorize a score of 7 or above as severe, in the Paul study a score of exactly 7 would still fall into the moderate category, while anything above a 7 would be classified as severe. The Paul study did, however, confirm Serlin's findings that the boundary between a mild and a moderate level of cancer pain is at 4 on a 0-10 numeric rating scale.[10]

The 1995 review by Jadad and Browman[49] (Figure 16) is key in shedding light on the usefulness and effectiveness of the WHO analgesic ladder for guiding cancer pain management. perform a systematic review of studies evaluating the effectiveness of the WHO analgesic ladder as an intervention for cancer pain management. The authors conducted a systematic critical review of studies that evaluated patients with cancer pain treated according to the WHO analgesic ladder. The study summarized eight case-series studies selected from among the following sources: MEDLINE from 1982 to 1995, hand search of textbooks and meeting proceedings, reference lists, and direct contact with authors. Jadad and Browman found that the studies suffered from several methodological limitations, and that analgesia was adequate in 69% to 100% of patients analyzed in the studies. They

conclude that it would be inappropriate to judge the performance of clinicians, programs, and institutions or to design policies based on evidence from the WHO ladder, because that evidence is insufficient to estimate confidently its effectiveness.[49]

E. Synopsis

In summary, longitudinal risks of pain, adequacy of analgesic treatment, racial/ethnic differences in the experience or burden of pain, determination of severity cutpoints on NRS pain measures, and the need for tumor-specific information are some of the problems in need of further study in the field of cancer pain research. Assessment and communication are not enough to effectively treat pain; evidence-based practices must be implemented in the treatment of pain.[106] This means that research should inform clinical practice in order to prevent worse pain outcomes over time among patients with cancer.

CHAPTER III

STATEMENT OF SPECIFIC AIMS

A. Study questions/specific aims

The over-reaching goal of this project was to better understand risks and risk factors for pain severity and interference outcomes over the course of disease among patients with metastatic breast cancer. Manuscript 1 addresses Aims 1 and 2 below, and Manuscript 2 addresses Aims 2, 3, and 4. We hope that this research will underscore the need for improvement in pain management strategies, and will provide tools to effect improvements in these strategies through better prediction of pain outcomes over time.

AIM 1: To provide descriptive epidemiologic information about pain hazards over time among patients with metastatic breast cancer, exploring the effect of using different intensity cutpoints on the Brief Pain Inventory (BPI) severity and interference 0-10 subscales with regard to baseline clinical and demographic covariates as risk factors.

Research question: What are the hazards of reaching different pain severity and interference thresholds over 51 weeks, and what baseline clinical and demographic factors are associated with occurrence of these outcomes?

AIM 2: To explore the relationship between the pain severity and interference BPI subscales with regard to sets of clinical and demographic covariates as predictors.

Research question: Given that the relationship between the severity and interference subscales of the BPI is nonlinear, how do clinical and demographic predictors compare in their associations with hazards over time for pain severity and interference outcomes?

AIM 3: To estimate the effects of both baseline and time-dependent clinical and demographic characteristics on time to first reaching a pain severity or interference score of 7 or above on the 0-10 BPI severity and interference scales.

Research question: How do baseline and time-dependent risk factors predict the outcomes of reaching a 7 or above on the BPI severity and interference scales?

AIM 4: To investigate the hypothesis that, as compared with their Caucasian counterparts, non-Caucasian patients would have worse longitudinal outcomes with regard to (a) pain severity, and (b) pain interference in daily functions.

Research question: Within our sample of longitudinal data collected in a clinical trial among patients with metastatic breast cancer, will our findings confirm existing findings of racial/ethnic disparities in the burden of pain? Also, with regard to hazards for these pain outcomes, how does the race variable fit in with other baseline and time-dependent clinical and demographic factors in a predictive model?

B. Hypotheses

In assessing risk of pain among different groups, we expected that those with lesser disease severity and better performance status at baseline (these lesser severity categories are: patients who are classified as "active" performance status at baseline, patients who have not had a previous skeletal complication [defined as experiencing one or more of the following: pathologic fractures, spinal cord compression with vertebral compression fracture, the need for surgery to treat or prevent pathologic fractures or spinal cord compression, or the need for radiation to bone[107]], patients with less time between bone metastasis and randomization, and patients undergoing hormonal therapy alone versus hormonal therapy adjunct to chemotherapy) would have lower hazards of experiencing severe pain earlier in the course of

treatment, lower hazards of experiencing pain severity and interference in the highest intensity categories (7 or above), and less severe experience of pain over time, as compared with their counterparts. This result was expected because as severity increases, so also do two potentially pain-causing factors: disease progression and the implementation of more aggressive multimodal treatment strategies. We expected that within a given 80-day interval, reductions over time in ECOG performance status would be concomitant with worse pain outcomes, as would having experienced any of the following since the last study visit: hospital admission, surgery, chemotherapy, or radiation. The temporality of these events within intervals, and their relationship with the timing of pain precludes conclusions about causality.

With regard to non-clinical covariates, we hypothesized that higher age would be associated with better longitudinal pain outcomes, and that membership in economically advantageous demographic categories at baseline: full-time employment, North American geographic region, college education, and most importantly, that Caucasian race would be associated with lower risk over time for pain severity and interference outcomes, as compared with their counterparts.

C. Rationale

The present study was designed to use longitudinally-collected pain data to address key gaps identified in current pain research. Through investigating our hypotheses and research questions in fulfillment of the specific aims described, our findings will help provide descriptive epidemiological information on pain hazards over the course of treatment among breast cancer patients, will justify or suggest changes to the cutoff points most commonly used in clinical practice today, and will explore the relationship between pain severity and

interference with daily functions. The tumor type under analysis for the present study, metastatic breast cancer, is common in relation to other tumor types, may exist in longstanding chronic forms, and is associated with high morbidity, mortality, and potential for pain, whether the pain is associated with disease and/or with treatment. These findings are also expected to aid those who treat breast cancer patients in identifying which patient characteristics and events are associated with greater risk for worse pain severity and interference outcomes. This knowledge can help clinicians target pain management strategies, tailor them to patient's risk factors, and better advise patients and patients' families on disease status, as well as on options for both cancer treatment and pain control. The long-term goal of this work is to aid in future clinical practice recommendations for treatment of pain in metastatic breast cancer.

CHAPTER IV

METHODS

A. Overview of methods

The present study was a retrospective cohort study that describes the longitudinal epidemiology of pain, assessed using the Brief Pain Inventory (BPI) among 1124 patients with metastatic breast cancer. We conducted a secondary data analysis of existing data from a clinical trial (Novartis protocol 4244603010) that assessed patient outcomes over at least 51 weeks. The "core phase" of the trial followed patients to 357 days, and an "extension phase" continued to follow patients beyond the core phase, such that patients who were receiving benefit from being in the trial would not be discontinued from the trial at the end of the core phase. Further details about the trial population are given below in the section entitled Subject identification/source population.

For Manuscript 1, we conducted proportional hazards analyses for reaching different thresholds of pain on the Brief Pain Inventory (BPI) severity and interference scales over time, comparing which sets of clinical and demographic baseline predictors affect hazards of reaching different thresholds of pain as defined by cutpoints on the 0 – 10 severity and interference scales. Patients reaching the intensity cutpoints of 3, 4, 5, 6, and 7 or above on each scale are the outcomes of interest in predictive modeling to analyze each cutpoint separately, then all cutpoints together, exploring interactions between covariates and cutpoints. Time-to-event was treated as continuous in these analyses. Sensitivity analyses address (a) how deaths are counted, and (b) handling of missing data.

For Manuscript 2, we estimated the effects of both baseline and time-dependent clinical and demographic characteristics on hazards for first reaching a pain severity or interference score of 7 or above on the 0-10 BPI severity and interference scales. We modeled the relationship between the two pain outcomes and sets of potential predictors using piecewise exponential models under an assumption of interval-censored time. Sensitivity analyses address (a) how deaths are counted, and (b) handling of missing data.

B. Study design

1. Subject identification/source population

The present retrospective cohort study was a secondary analysis of existing data from a clinical trial (Novartis protocol 4244603010). Informed consent was obtained from each patient in the original trial, and the multicenter trial was carried out under approval from each institution's ethical review board, in accordance with applicable laws in each country and the Declaration of Helsinki. The secondary analysis in the present study was conducted under approval from the University of North Carolina at Chapel Hill Institutional Review Board. The trial assessed patient outcomes over at least 51 weeks using the Brief Pain Inventory (BPI)[108] to measure pain among 1,648 patients with metastatic breast cancer or multiple myeloma. Saad et al.[109] provide a full report of the primary analyses of the double-blind, multicenter clinical trial, the purpose of which was to compare two bisphosphonate drugs, intravenous zoledronic acid [4 or 8 mg] versus intravenous pamidronate disodium [90 mg], as an adjunct to standard therapies, in the treatment of multiple myeloma and breast cancer patients with cancer-related bone lesions. No placebo arm was used. The intent-to-treat (ITT) study population consisted of men and women with stage III multiple myeloma (n = 510) or

stage IV breast cancer with ≥ 1 lytic or mixed bone metastasis (n = 1130). For the purpose of the present analysis, we limited the sample to women with breast cancer (n = 1124).

a. Trial inclusion/exclusion criteria

Patients were included in the trial if they had a histologically confirmed diagnosis of breast cancer with at least 1 bone metastasis confirmed by conventional radiographs of bone (plain film); were ambulatory; were aged at least 18 years; and had an ECOG performance status of less than 3 (see the Predictors section for more information about this variable). Patients were required to be receiving antineoplastic therapy at the time of randomization and to be in good clinical condition. Patients receiving hormonal therapy for breast cancer had to be on first- or second-line hormonal therapy for metastatic disease. They could not be receiving greater than second-line hormonal therapy for metastatic disease, except in combination with chemotherapy. Patients were excluded from the trial if they were pregnant; had undergone treatment with bisphosphonates at any time during the 12 months prior to visit 1 (unless limited to a single dose administered at least 14 days prior to visit 1); had breast cancer with lymphangitic lung metastases; had clinically symptomatic brain metastases; had been treated with other investigational drugs within 30 days prior to randomization; had a history of noncompliance to medical regimens or potentially unreliable behavior (e.g., alcoholism, psychosis, drug addiction); or had heart disease meeting grade III or IV of the New York State Heart Association functional classification.

b. Trial stratification, geography, and timeframe

The sample was stratified at enrollment into two categories: (1) patients with breast cancer undergoing chemotherapy or breast cancer patients undergoing both chemotherapy *and* hormonal therapy, versus (2) patients with breast cancer undergoing first-line or second-

line hormonal therapy without chemotherapy. These stratification categories were used as covariates in the present study. The clinical trial was conducted at 207 centers in the following countries (grouping identified in parentheses): Canada and the United States (North America); Argentina, Brazil, Chile, Peru, and Uruguay (South America); Austria, Belgium, the Czech Republic, France, Germany, Ireland, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, and the United Kingdom (Europe); and Australia, Israel, New Zealand, and South Africa (other). The first patient was recruited on October 16, 1998, and the last assessment was completed on the last patient on January 12, 2001.

2. Measurement, assessment, and validity

    a. Outcomes: pain severity and interference

Patients completed the Brief Pain Inventory questionnaire (see Appendix B) according to the trial data assessment schedule shown in Figure 18.

Figure 18. Trial data assessment schedule (BPI and ECOG measurements).

Months		0				3				6				9				12	
Days	-14	0	21	42	63	84	105	126	147	168	189	210	231	252	273	294	315	336	357
Weeks	-2	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Visits	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
ECOG		x				x				x				x					x
BPI		x	x	x		x		x		x		x		x		x		x	x

Patients completed the Brief Pain Inventory questionnaire at baseline, months 1 and 2, and every other month thereafter up to months 12 and 13 (Weeks 50 and 51). The BPI was administered in person before the patient was interviewed by the physician or received study

medication. The Brief Pain Inventory (BPI) measure consists of several parts, but this study uses only the pain severity and interference items. Severity was measured as: average pain, pain right now, worst pain, and least pain, all four of which are answered on a 0-10 scale, with 0 = “no pain” and 10 = “worst pain imaginable”. The "worst pain" or the arithmetic mean of the 4 severity items can be used as measures of pain severity. For the present study, at the advisement of the BPI instrument’s creators, we use the arithmetic mean of the 4 severity items rather than the “worst pain” score alone. The BPI includes a 7-item pain Interference scale, which consists of the same 0-10 response scale to the question: “describe how, during the last 7 days, pain has interfered with your: 1) general activity, 2) mood, 3) walking ability, 4) normal work (includes both work outside the home and housework), 5) relations with other people, 6) sleep, and 7) enjoyment of life. The arithmetic mean of the 7 interference items was used to measure pain interference.

In general, numeric rating scales for pain severity such as the BPI have been demonstrated to be valid and sensitive to change.[110] According to the American Pain Society Clinical Practice Guideline for the Management of Cancer Pain in Adults and Children,[18] NRS measures are among the most common, valid, and reliable measures used to assess cancer pain severity, and are preferred by patients over VAS measures. The BPI has been administered and assessed for validity in several languages including Spanish, French, Japanese, Chinese, Italian, Hindi, German, Greek, and Vietnamese.[34-40]

In a key study of clinically meaningful change for the BPI, Farrar and colleagues[43] conducted a validation study in 134 cancer patients that concluded that the minimally important difference (MID) was a change or difference of 2 or more points in a generic numeric rating scale of pain intensity that (like the BPI) ranged from 0-10. The clinical

anchor for "important difference" in their study was the outcome of whether additional pain medication was needed 30 minutes after a first dose of pain medication was given (i.e., the successful treatment of pain). The authors zeroed in on the 2-point difference using the maximized sensitivity and specificity from the results of their receiver operating characteristic (ROC) curve analysis.

b. Predictors: clinical and demographic variables

In addition to the pain assessments, subjects were asked to provide demographic, clinical, and outcomes information through interviews, written questionnaires, and physical examinations, to complete the clinical case report form and other original clinical trial source documents in accordance with the study protocol. Analyses comparing treatment arms as predictors have already been conducted and are reported elsewhere.[111] Comparisons between the treatment arms are not a part of the present study because the two comparative treatments were not found to affect pain in the report of the clinical trial results by Rosen et al. (2001).

For the present analyses, we group all the patients together to compare them with regard to clinical and demographic characteristics. These characteristics included ECOG performance status [1 = active (ECOG status of 0 or 1), 0 = restricted (ECOG status of 2 or above)], age, education (1 = college degree, 0 = no college degree), employment status (1 = full-time, 0 = other), geographic region (North America, South America, Europe, or Other – defined previously per-country), antineoplastic therapy on study entry, analgesic therapy, previous skeletal complications (0 = no, 1 = yes), and dates of initial cancer diagnosis, initial metastasis, initial metastasis to bone, and disease progression. On the ECOG status data collection form, Karnofsky Performace Status (KPS) anchors are given as follows. ECOG status = 0 (KPS = 90-100); ECOG status = 1 (KPS = 70-80); ECOG status = 2 (KPS = 50-

60); ECOG status = 3 (KPS = 30-40); and ECOG status = 4 (KPS = 10-20). Skeletal-related events (SREs) were defined in the trial as one or more of the following: pathologic fractures, spinal cord compression with vertebral compression fracture, the need for surgery to treat or prevent pathologic fractures or spinal cord compression, or the need for radiation to bone.[107]

In several cases, we recoded baseline covariates as dichotomous in order to facilitate modeling techniques. Caucasian race, college education, full-time employment, age, and North American geographic region were dichotomized as such for this reason. We coded the full-time employment and college education variables (each of these variables had about 16% missing data at baseline) as three-level categorical variables, with the categories as "yes", "no", or "missing", with "yes" as the referent so that the effect of lower educational attainment or no employment could be assessed. This technique prevents these observations from being dropped from the models. Age was normally distributed, and dichotomized for Manuscript 1 at its mean of 57.9 (SD ±12.7). The lower age category was 24-57, and the higher age category was 58-95. The age variable was continuous in decades for exploratory analyses in Manuscript 1 and for Manuscript 2.

Time-dependent characteristics included in the present study were performance status over time (also measured by ECOG performance status with the same dichotomous categorization described above), surgery since the last study visit, chemotherapy treatment since the last study visit, and radiation treatment since the last study visit. The trial visit schedule shown in Figure 18 displays when ECOG performance status data were collected throughout the trial.

C. Methods

1. Data preparation

   a. Coding

For the purposes of these analyses, we recoded several variables. Race, education, employment, and geographic region were dichotomized; Table 3 describes the coding scheme for each of the variables used in the analysis.

Table 3. Variable coding/recoding scheme

Variable name	Label	Type	Code	Source / derivation (if applicable)
SBJ1N	Subject number	num	-	
VIS1N	Visit Number	num	-	Inclusion/Exclusion by VIS1N: Keep records where 2 LE VIS1N LT 20 or 97 LE VIS1N LT 99
DAYSRAND	Days from randomization Imputation 1	num	-	= LSTDATE - V2DATE If maximum VIS1N for a patient is LE 19
LSTDATE	Last date patient observed	DATE11	-	
V2DATE	Date of randomization	DATE11	-	
PAINDTE	Date of BPI assessment	DATE11	-	

Variable name	Label	Type	Code	Source / derivation (if applicable)
BPITIME	BPI Days since Rand	num	-	= PAINDTE - V2DATE if 2 LE VIS1N LT 20 or 97 LE VIS1N LT 99 Note: If BPITIME is negative, set equal to 0.
AGE1N	Age in years	num	-	-
RCE1C	Race	num	-	1 = 'Caucasian' 2 = 'Black' 3 = 'Oriental' 4 = 'Other';

CAUC	Caucasian race	num	0 = not cauc.
			1 = caucasian
				if RCE1C = . then cauc = .; (not applicable because no data are missing for race)
				else if RCE1C = 1 then cauc = 1;
				else if RCE1C in (2,3,4) then cauc = 0;

COU1A	Country	char	-	-

Variable name	Label	Type	Code	Source / derivation (if applicable)
GEOG	Geographic Region	char	NA = North America SA = South America EU = European Union	=NA If COU1A = USA or CDN = SA If COU1A = BR, PE, RA, RCH or U = EU If COU1A = A, B, CH, CZ, D, E, F, GB, I, IRL, NL, PL, or S
			O = Other	= O If COU1A = AUS, IL, NZ, or ZA
GEOGNA	Dichotomous geographical region	num	0 = Not North America 1 = North America	if GEOG = 'NA' then geogna = 1; else if GEOG ne 'NA' then geogna = 0;
PREVSRE2	Previous SRE	num	0 = None 1 = Previous SRE	
STRAT_E	Strata for Efficacy analysis	num	1='Multiple myeloma' 2='Breast cancer with chemo' 3='Breast cancer with hormonal'	
CHEMO	Chemotherapy at baseline	num	if strat_e = 2 then chemo = 1; else if strat_e = 3 then chemo = 0;	

Variable name	Label	Type	Code	Source / derivation (if applicable)
P_REASON	Study completion form – primary reason for premature discontinuation	num	1 = Adverse event(s) (also specify on the Adverse Events form) 2 = Abnormal laboratory value(s) 3 = Abnormal test procedure result(s) 4 = Unsatisfactory therapeutic effect 5 = Subject's condition no longer requires study drug 6 = Protocol violation 7 = Subject withdrew consent 8 = Lost to follow up 9 = Administrative problems 10 = Death (please complete Serious Adverse Events form and record adverse events leading to death on the Adverse Events form)	
DATEDIED	Date of death	DATE11	Date of death	

Variable name	Label	Type	Code	Source / derivation (if applicable)
ECOG	ECOG Performance Status (Raw)	num	0 = Fully active 1 = Restricted 2= Ambulatory 3 = Limited self-care 4 = Disabled 5 = Dead	= ECOG at each visit
BECOGA	Active ECOG baseline Y/N	num	0 = Restricted 1 = Active	if baseline ECOG (interim variable base_ecog = ECOG at first visit) in (0,1) then becoga = 1; else if base_ecog = . then becoga = .; else if base_ecog in (2,3,4) then becoga = 0;
SURG_	Surgery since last visit	num	0 = No 1 = Yes	
RAD_	Radiation since last visit	num	0 = No 1 = Yes	

Variable name	Label	Type	Code	Source / derivation (if applicable)
CHEM_	Chemotherapy since last visit	num	0 = No 1 = Yes	
ADMIT	Hospital admission since last visit	num	0 = No 1 = Yes	
WPAINL7D	Worst pain	num		-
LPAINL7D	Least pain	num		-
APAINL7D	Average pain	num		-
PAINNOW	Pain now	num		
BPIC	BPI Severity Composite Score	num		= Average of WPAINL7D, LPAINL7D, APAINL7D, PAINNOW if none of these 4 = .
GENACT	Interference in general activities	num		-
MOOD	Interference in mood	num		-
WALK	Interference in walking ability	num		-
WORK	Interference in normal work	num		-

Variable name	Label	Type	Code	Source / derivation (if applicable)
RELATION	Interference in relations with other people	num		-
SLEEP	Interference in sleep	num		-
ENJOY	Interference in enjoyment of life	num		-
INTERFERE	BPI Interference composite score	num		= average of GENACT, MOOD, WALK, WORK, RELATION, SLEEP, ENJOY (if at least 4 of these are nonmissing - if 4 or more are missing, Interfere = .)

Note: LT = less than. GT = greater than. LE = less than or equal to. GE = greater than or equal to. NE = not equal to. Rand = randomization. Num = numeric. Char = character. Single dot "." indicates missing value in SAS.

b. Exploratory analysis

We examined each categorical predictor variable for its frequency distribution and extent of missing data, and each continuous predictor and continuous outcome variable for its normality distribution, skew, kurtosis, and outliers, in order to select the appropriate statistical tests. Exploratory analyses assessed how the baseline characteristics and outcomes differed by race at the time of randomization.

c. Bias, confounding, and effect measure modification

Self-selection and diagnostic bias for participation in clinical trials should always be acknowledged as a threat to external validity when extrapolating findings, since those who participate in the trial may not represent the population to which one wishes to generalize. The large trial population of 1,124 patients may be considered a strength of the present study, assuming minimal impact of potential bias due to the sampling methods on this sample's representativeness of women with metastatic breast cancer. Early research on how clinical trial participants differ from non-participants suggests that trial participants have less mortality than non-participants.[112] In their 2004 study of cancer clinical trial participation, Murthy and colleagues found that younger and minority patients were less likely than their counterparts to participate in cancer clinical trials.[113] However, the distribution of race in this study (recorded as "Black" for 5.7% of the sample) appears close to the distribution of race among prevalent first malignant breast cancer cases in 2002 in the U.S. (Black = 7.4% of total cases) estimated by Surveillance, Epidemiology and End Results (SEER).[114] With regards to age, women aged 57 years or less composed approximately half the trial population, while 20% of prevalent breast cancer cases were aged 54 or lower in 2002 U.S. estimates (27-year limited-duration prevalence, first malignant cancer only).[114] Thus, both the age and race distributions in the present study seem to roughly approximate the populations to which we would generalize the findings, although the influence of potential bias with regard to traits affecting pain outcomes cannot be ruled out entirely.

Because this was a cohort study, information bias would be of concern if the outcome of perceived pain were misclassified with respect to any of the covariates. Patients may

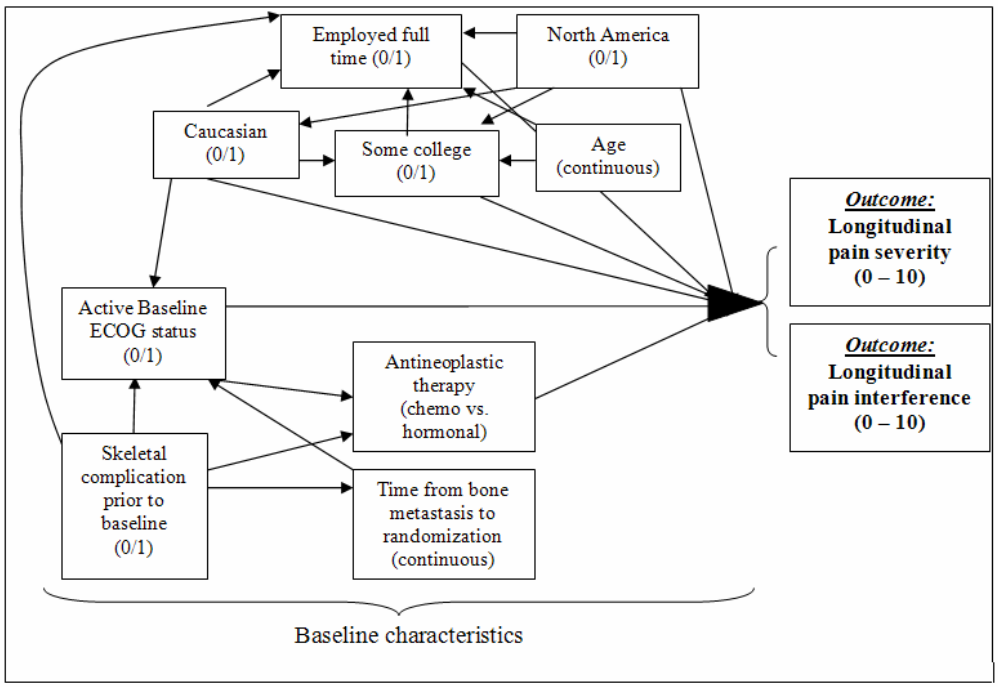
underreport or overreport the pain they experience. Although underestimation of pain is more a problem in retrospective studies involving spontaneous patient reports,[30] it is still possible that in the present study, patients may underreport pain (there is more evidence for underreporting, rather than overreporting, being a likely problem). Based on cultural views, some patients may believe that pain is a spiritual or religious test of their faith, or believe that it is wrong to take or become addicted to opioids. These patients may therefore refuse to report their pain or accept palliative treatment.[31] When interpreting the results of the present study, we acknowledge that, due to potential and probable underreporting,[30,31,115,116] our estimates may be biased downward toward lower amounts of pain than patients actually experience. Misreporting of pain is a problem that could vary with respect to the covariates, but without having a "true" score to compare with the reported score for any patients in the study, the magnitude and/or direction of this potential bias cannot be known. Clinicians and researchers must rely on patient report of pain, since no neurophysiological or laboratory test can measure pain.[117] However, it is possible to measure and estimate the extent of misreporting, and to educate patients such that they would be more likely to report the truth in the goal of receiving the most appropriate treatments. Potential bias from differential item functioning in the present study could lead to either under- or over-estimation of effects with regard to their true values.

Because bisphosphonates have been found to reduce skeletal events and bone pain in advanced breast cancer where bone metastasis is present,[62] it is useful in interpreting the findings of the present study to keep in mind that all of the patients under study (i.e., both treatment arms) were being treated with bisphosphonates and adjuvant standard therapy. The

effect of the entire study sample undergoing bisphosphonate treatment in the present study would be that pain may be underestimated in this sample as compared with patients undergoing standard therapy alone.

Predictive modeling methods do not assess the effect of a specific exposure or treatment upon the outcome of interest. Traditional epidemiologic methods for assessing confounding under the overarching goal of assessing an exposure – outcome relationship do not apply because the goal of predictive modeling is to identify those factors that account for the most variance in the model being fit to describe the outcome, and further, to build the most parsimonious predictive model possible.[118,119] Instead of using a directed acyclic graph (DAG) with identification of unblocked backdoor paths, for the present study we sought to diagram possible theoretical associations between the set of variables being studied and the outcomes. Figure 19 is a schema that represents a preliminary exploratory analyses of possible associations among the covariates and the outcomes. Indeed, most all of the covariates could feasibly be associated with the others, and most covariates could feasibly be directly associated with pain outcomes.

Figure 19. Explanatory covariates; relationships with each other and with the outcomes.



Unlike confounding, effect measure modification may still be assessed in predictive models. The covariates were assessed for potential effect measure modification through testing the inclusion of interaction terms in the modeling processes, using likelihood ratio tests to compare models with and without interaction terms. Where effect measure modification was found to be present, stratified results are reported.

d. Power calculation

To calculate the respective sample sizes that would be needed to detect a statistically significant change in the BPI intensity scale, a simple change-from-baseline approach was used to compute the mean and standard deviation of change scores; the change-from baseline method was used only for the purpose of power calculation. Change scores were computed only for those who have a BPI score at both visit 10 (24 weeks post-randomization) and at baseline. Clinical meaningfulness of change scores is not considered in the sample size

calculations, which are geared instead toward statistically significant changes on the scale. The simplified sample size calculation method involving a calculation of change scores is the current standard for longitudinal studies, and is deemed acceptable but not ideal, in consideration of current software limitations that do not yet fully accommodate longitudinal data structures (Personal communication, Gary Koch, March 2005). The power calculation is thus geared toward the hypothetical estimation of a statistically significant difference in change scores between the exposure groups in each type of cancer. In terms of precision, the 95% confidence intervals (CIs) around point estimates would be too imprecise if they included the next integer (e.g., the 95% CI around a baseline estimate of 7.0 should not include 8.0). In this calculation, we use as the exposure the covariate of chemotherapy treatment versus hormonal therapy alone.

An alpha of 0.05 was used in the sample size calculations, in accordance with current conventions. A beta of 99% is desirable when using clinical trials data, however, power to detect statistically significant differences in change scores was the main outcome of the sample size calculation, since sample sizes are already fixed. Based on preliminary analyses of the clinical trial data, the expected mean BPI score at baseline should be similar for both groups for each anchor measurement at baseline, and should be above 3.0 (a mean derived from a population of cancer patients which was not constrained to those being treated for pain specifically), with an expected standard deviation of BPI scores at baseline of ± 2.17 points.

Parameters for these sample size calculations were as follows:

- Two-tailed alpha of 0.05 for both 2-group comparisons. The basis for this significance criterion is the acceptance in accordance with convention of a 5%

probability of rejecting the null hypotheses (that BPI change scores did not differ between each of the two groups).

- Power = the outcome of interest for the sample size calculations, since sample sizes are fixed in this secondary data analysis design.
- SD of BPI change scores = ± 2.22 for breast, ± 2.11 for prostate. Numbers of patients in each exposure category are shown below.
- Correlation between levels (over repeated assessments) of BPI scores = 0.57 (based on unpublished analyses of longitudinal BPI data)
- Sample size estimates assume no dropout
- The sample size formula used was for independent samples *t*-tests. The effect sizes entered into the formula were entered and varied according the benchmarks for effect size described below. As stated in nQuery (version 3.0),[120] the effect size is an index of the separation expected between the observed means in the two groups.

Table 4. nQuery analysis: chemotherapy as exposure

Exposure groups n(%):		
Breast cancer with chemotherapy	525	(46.71)
Breast cancer with hormonal treatment	599	(53.29)

Change scores:			
N	789	Sum Weights	789
Mean	-0.57	Sum Observations	-452.58
Std Deviation	2.22	Variance	4.95

Cohen's benchmarks for effect size[121] were used for this sensitivity analysis of sample sizes needed. Effect sizes of 0.2, 0.5, and 0.8 may be characterized as small, medium, and large, respectively. Above 0.8 may be considered a very large effect size, and is shown below

because the expected difference in means of 2 points would correspond with a minimally important difference (2-point expected difference in means).

Table 5. Power calculation: sample sizes needed to detect differences in means

Expected difference in means	Unadjusted ES (= Mean diff / SD of 2.22)	Power (%)[120]
0.44	0.20	91
1.11	0.50	99
1.78	0.80	99
2.00 (MID)	0.90	99

Note: Unadjusted ES assumes no within-group correlation of change scores.

For each effect size based on mean change scores, the sample sizes shown in Table 4 would be needed to test this range, in accordance with the parameters shown in Table 5 (ES = effect size, SD = standard deviation, MID = minimally important difference).

2. Statistical analysis

We conducted the analyses using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) and SAS-callable SUDAAN Release 9.0 (Research Triangle Institute, Research Triangle Park, NC, USA). All analyses were conducted on the ITT sample, which included all female breast cancer patients who had been randomized in the trial. We calculated descriptive statistics and assessed extent of missing data for the predictor and outcome variables under study. These analyses were performed under two possible assumptions about the data: that time in the model was continuous versus categorical (also called "interval-censored"). The analyses for Manuscript 1 (MS1) assessed the relationship of baseline predictors with time to reach pain cutpoints 3, 4, 5, 6, or 7 on the 0-10 severity and interference scales, under a

model with a continuous time assumption. The analyses for Manuscript 2 (MS2) assessed the relationship of baseline and time-dependent covariates on the outcome of reaching a 7 or above on the severity or interference scales, under a model with categorical time assumption.

a. Baseline predictors of hazards for severity and interference scales: analyses of multiple cutpoints (MS1)

Time-to-event was calculated as the number of days from randomization until the patient reported reaching a given severity cutpoint (3, 4, 5, 6, or 7) on the BPI. For each cutpoint, those who never reached that cutpoint as of trial completion (51 weeks, or 357 days, post-randomization) or dropped out of the study were classified as censored. For censored patients, the event indicator variable was set to 0, and time at risk was the time from their randomization date to trial completion or dropout.

We used visual examination of Kaplan-Meier (KM) curves along with the log-rank test statistic to assess the candidacy of each covariate for stepwise univariate modeling. Covariates for which the KM curves did not cross and the log-rank test was significant at a criterion of $\alpha = 0.05$ were considered best candidates as potential explanatory variables for inclusion in the Cox proportional hazards models. Continuous covariates were dichotomized at the mean if normally distributed, or at the median if non-normally distributed, for the purposes of the KM curve analysis and to be used as dichotomous predictors. Age was normally distributed, and dichotomized for the multivariate analyses at its mean of 57.9 (SD ±12.7). This resulted in age categories of 24-57 and 58-95 years. Days from bone metastasis to randomization was non-normally distributed, and dichotomized at its median of 104 days (interquartile range = 36 to 475 days).

Time-to-event model building techniques were conducted with the goal of creating parsimonious predictive models to determine the covariate-adjusted hazards of reaching each cutpoint over time. These techniques relied on the stepwise procedure with model entry specified at 0.25, and staying criteria specified at 0.15. The univariate Cox proportional hazards models are expressed as follows:

$$h(t \mid \boldsymbol{X}) = h_0(t)e^{\left(\sum_{k=1}^{p}\beta_k X_k\right)}$$

where $h(t \mid \boldsymbol{X})$ is the hazard for an individual with covariate set $\boldsymbol{X}$, $h_0(t)$ is the non-specified baseline hazard function (when all $X_k = 0$), p is the number of explanatory variables, and $e^{\left(\sum_{k=1}^{p}\beta_k X_k\right)}$ is a known function.

To analyze the time until first reaching each cutpoint explored (3, 4, 5, 6, and 7 on the 0-10 scale) simultaneously with the same explanatory covariates, we fit multivariate Cox proportional hazards models using PROC SURVIVAL in SUDAAN, which implements a Taylor series variance estimation to account for within-subjects correlation between multiple possible outcomes. The explanatory variables used as baseline predictors were ECOG performance status, age, race, college education, full-time employment, and previous skeletal related event. We chose this set of explanatory variables for the multivariate model because these factors had emerged as most consistently influential across the univariate analyses. In the multivariate model, each patient had several potential outcomes: time to 1st reaching the score of each cutpoint (3, 4, 5, 6, and 7) or higher on the 0-10 scales. To model these outcomes simultaneously, we fit the Cox proportional hazard model as follows:

$$h_j(t) = h_0(t)e^{\alpha_j + \sum_{k=1}^{p} \beta_{jk} X_{jk}}$$

where j = 3, 4, 5, 6 or 7 for the different pain score cutpoints. This equation applies to any patient i. We assume proportional hazards across different outcomes reflected by a constant α_j. β_{jk} can be the same for different outcomes.

In univariate and multivariate models, the exponentiated individual parameters, e^{β_k}, are the hazards. In comparing hazards with each other, hazard ratio (HR) values greater than 1.0 imply a significantly higher hazard of reaching a given pain endpoint relative to the reference group, if the confidence interval excludes the null value at a significance criterion of α = 0.05. We used only the baseline assessment of all the clinical and demographic covariates described. Therefore, each variable in this set of p covariates was considered time-independent in the models.

b. Hazards model for time to first occurrence of a 7 or above, categorical time assumption, incorporation of time-dependent covariates (MS2)

For both the clinical and statistical interest of cutpoint 7 on the BPI, we chose to model the hazards for time to first occurrence of a 7 or above on each scale. The trial data assessment schedule involved visits scheduled every 21 days, with BPI assessments every 2 visits and ECOG assessments every 4 visits. The pain severity questions were asked over the timeframe of the past seven days (with the exception of "describe your pain right now") and the pain interference questions were asked over the timeframe of the past 24 hours. This means that gaps in information as long as 5 weeks exist in the severity data, and even longer gaps exist in the interference data. Given these gaps in information, the present study involved interval-censored data because a patient could have experienced an event between

two assessments but the exact date of the event is unknown. Interval-censored data may be analyzed under an assumption of categorical rather than continuous time at risk for hazards models. We handled this assumption using a piecewise exponential model (using PROC GENMOD) with categorized time in Poisson regression. As adapted from Stokes, Davis and Koch, *Categorical Data Analysis using the SAS System* (2000), the piecewise exponential likelihood for the present models, with continuous covariates, is as follows:

$$\Phi_{PE} = \prod_{i=1}^{n} \prod_{k=0}^{m_i} \lambda_{ik} \left\{ \exp\left[-\lambda_{ik}^{y_{ik}} N_{ik} \right] \right\}$$

where y_{ik} is equal to 1 if the event occurred, or 0 if the event did not occur for the *i*th person during the *k*th interval, N_{ik} is the total person-time of exposure (in days), m_i is the maximum number of intervals for subject *i*, and λ_{ik} is the hazard parameter. The piecewise exponential model assumes that there are conditionally independent exponential distributions with hazard parameters λ_{ik} for the respective time periods.[122] The properties of this method enable us to obtain effect estimates from Poisson regression computations using the assumption of the piecewise exponential model, regardless of whether we make the conditional arguments necessary to assume a Poisson distribution. Stokes and colleagues (2002) discuss these specific properties further.[122]

For the categorical data analysis, intervals were assigned as every 80 days following randomization, with a total of 5 intervals. Intervals were numbered 0 through 4, with the last interval beginning 320 days following randomization, and ending at 400 days (57 weeks) following randomization. Interval 0, also called the "first interval" was the referent and was 80 days in length. Although the choice of interval length and number of intervals can be completely arbitrary for the piecewise exponential model to still be valid,[33] we chose the 80-

day interval length based on the distribution of events in the intervals; model convergence requires a minimum number of events in any given interval.

For any interval in which a patient remained in the study but did not reach the outcome, time at risk was set at 80 days. A patient's last interval was the interval in which she (a) reached the outcome of a 7 or above, (b) dropped out before the 400-day mark, or (c) died before the 400-day mark. For those who reached the outcome, in their last interval an event indicator variable was set to 1, and time at risk was defined as the time from the beginning of the interval to the date of the report of a 7 or above. For patients who dropped out early or died, time at risk in the last interval was equal to the number of days from the beginning of the last interval to the date of dropout or death. If a patient never reached the outcome in *any* interval, that observation was censored, such that the event indicator variable was set to 0 for all intervals, and time at risk within each interval was assigned as 80 (or, in the cases of dropout or death, the time at risk in the last interval would be the number of days from the beginning of their last interval to the date of dropout or death).

To account for within-subjects correlation of multiple outcome assessments over time, we used generalized estimating equation (GEE) methods to adjust the standard errors and confidence intervals around the estimated model parameters. We assessed model fit by evaluating the significance at a criterion of $\alpha = 0.05$ of the Residual χ^2 score statistic for contribution of covariates and all possible time-by-covariate interaction terms not included in the model.

c. Exploring the severity-interference relationship (MS1 and MS2)

These data presented an opportunity to explore the relationship between the BPI intensity composite score and the BPI interference composite score. Both scales are rated numerically

on a 0-10 scale, with 10 indicating greatest severity or interference. To explore the relationship of these two subscales, we explored the similarities and differences in how sets of explanatory covariates affected pain severity versus interference outcomes.

d. Sensitivity analyses

Handling deaths in the analysis (MS1 and MS2)

An overarching issue that affected all the survival analyses was that in the analyses, death may be dealt with either by: 1) censoring, or 2) treating death as an event of the worst possible outcome (severe pain).[123] We conducted a sensitivity analysis to address this issue. For those individuals who died, instead of censoring their observation, we assigned time to reach severity of 7 or higher at the time of death as if death were comparable to a BPI score of 10, and the time of death was the last time for pain assessment. The dropout date was effectively either the last day of enrollment in the trial, or the last day the BPI was administered, whichever was the later of the two. We compared the model results using this technique with those results from conventional censoring.

Counting days from randomization to event (continuous time assumption) (MS1 and MS2).

The analysis methods required that we make certain assumptions about handling the event indicator and time at risk variables, given missing data scenarios present in the data. There were four possible such scenarios, for which we implemented the following coding for event indicator and time-to-event variables:

- (Scenario A) if a patient reached a BPI measurement of [3,4,5,6, or 7] (hereafter referred to as “the outcome”) then the dichotomous event indicator variable was set

equal to 1 and time at risk was set equal to the number of days from randomization to the date of the first occurrence of the outcome.

- (Scenario B) If the patient had complete BPI data but never reached the outcome, then the dichotomous event indicator variable was set equal to 0 and time at risk was set equal to total number of days the patient was in the study (leading to these observations being censored in the survival analysis).
- (Scenario C) If a patient did not have any BPI data then the patient was not included in the survival analysis.
- (Scenario D) If the patient had some BPI data but never reached the outcome, then the dichotomous event indicator variable was set equal to 0. The observation was censored as in Scenario B, but total time at risk was set equal to either the total number of days the patient was in the study (assumption D.i), or to the number of days from randomization to the date of the preceding non-missing BPI measurement (assumption D.ii). We conducted a sensitivity analysis to assess the impact of different missing data handling methods, using these two variations of Scenario D (D.i and D.ii).

Another missing data handling technique used was to code the full-time employment and college education variables (each of these variables had about 16% missing data at baseline) as three-level categorical variables, with the categories as "yes", "no", or "missing", with "yes" as the referent so that the effect of lower educational attainment or no employment could be assessed. This technique prevents these observations from being dropped from the models.

3. Quality assurance/quality control

    a. Outcome scoring

The BPI scoring rules were quality-control checked by hand for correct calculation, as well as to make sure that all reverse-scored items were properly reversed. Three people separately carried out quality control (QC) checks on subsets of randomly chosen observations, with each subset representing a scoring situation with possible error potential, and several observations in each subset.

    b. Recoding

For variables that were recoded (for example, a multi-level categorical variable such as ECOG status being dichotomized to active versus inactive for the present analyses), the recoding was verified using SAS to cross-tabulate the new and old variables, including display of missing values, using the following code: "PROC FREQ; tables [original variable] * [new variable] / missing". I examined each cross-tabulation to make sure that there were no errors created in the recoding process, and had a second person verify the cross-tabulations.

    c. Data restructuring

For the survival analyses conducted under the continuous time assumption, it was necessary to convert the original dataset from multiple observations/records per patient (each visit constituting a separate observation within a given subject's multiple records), to a structure with only one record per patient, with multiple assessments over time reflected as separate variables within the single record. Event indicator and time-to-event/time-at-risk variables were created using the data restructuring methods described in Allison (1995)[124] and in Stokes, Davis, and Koch (2000).[122] We checked the accuracy of each restructuring by comparing before and after printouts at each phase, cross-checked by a separate programmer

who examined the records as well as the data restructuring code in SAS. In addition, we implemented these same QC procedures to check the creation and coding of indicator variables and time-at-risk variables. The same QC and accuracy checking procedures were implemented when data had to be restructured (e.g., one observation per cutpoint per patient or one observation per interval per patient) for the survival analyses.

d. Primary data (clinical trial)

For clinical and demographic data, the pharmaceutical sponsor used a Contract Research Organization (CRO) to conduct data quality checks and queries as follows: Data items from the data collection forms (case report forms, or CRFs) were entered into the study database (Clintrial version 3) at the CRO, using double data entry with verification upon second entry. Text items (e.g. typed comments) were entered once and checked manually against the CRFs. Subsequently, the information entered into the database was systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious data entry errors were corrected by CRO personnel. Other errors or omissions were entered on Data Query Forms, which were returned to the investigational site for resolution based on source documentation. A copy of the signed Data Query Form was kept with the CRFs, and once the original was received at the CRO, the resolutions were entered into the database. QC audits of all key safety and efficacy data in the database were made when the last query from an individual patient was returned.

CHAPTER V

RESULTS

A. Manuscript 1: Pain Severity and Interference Hazards, with Exploration of BPI Cutpoints, Among Women with Metastatic Breast Cancer

ABSTRACT

Background. Knowledge about risk factors for cancer pain over the course of disease in specific tumor types is limited. This study assesses pain hazards over time among patients with metastatic breast cancer. We identify risk factors for worse pain outcomes over time and explore the effect of using different intensity cutpoints on the Brief Pain Inventory (BPI) severity and interference with daily living 0-10 subscales, as related to baseline clinical and demographic characteristics.

Methods. We conducted proportional hazards analyses of existing data from a clinical trial that assessed patient outcomes observed at 11 visits over 51 weeks using the BPI to measure pain among 1124 patients with metastatic breast cancer. Univariate (per-cutpoint) and multivariate (cutpoints 3, 4, 5, 6, and 7) models were used to estimate hazards for time to reach each outcome on the BPI severity and interference scales. The sets of clinical and demographic baseline explanatory variables were then compared among the models.

Results. In multivariate analyses of the severity scale, compared with Caucasian race, non-Caucasian race was associated with 2.29 times the hazard of reaching severity cutpoint 7 versus 1.38 for cutpoint 3, all other covariates held constant. For the interference scale, compared with active baseline Eastern Cooperative Oncology Group (ECOG) status, restricted baseline ECOG status was associated with 2.97 times the hazard of reaching

interference cutpoint 7 versus 2.00 for cutpoint 3, all other covariates held constant. Other baseline factors associated with higher hazard of reaching higher scores on the severity scale were: restricted baseline ECOG performance status, previous skeletal related event (SRE), and not employed full-time (hazard ratios [HRs] = 1.70, 1.23, and 1.33, respectively). College education and age dichotomized at 57 years did not appear to have independent influence on the severity scale. Other predictive factors on the interference scale were: non-Caucasian race, previous SRE, age ≤ 57 years, and not employed full-time (HRs = 1.40, 1.20, 1.39 and 1.45, respectively). College education did not appear to affect pain on the interference scale.

Conclusions. Our findings that non-Caucasian race, younger age, and restricted baseline performance status are important predictors of pain over time are consistent with previous cross-sectional risk factor studies and with clinical practice. ECOG performance status and race are of key prognostic importance. In confirming these characteristics as predictors of pain hazards over time in women with metastatic breast cancer, our findings inform individualized prognoses for pain outcomes according to baseline patient attributes. Early intervention and more aggressive pain management strategies can be tailored to these personalized prognoses over the course of treatment, to delay first occurrence of higher pain scores among those at greatest risk for severe pain and pain interference in daily activities.

1. Introduction

Epidemiologic inquiry into the course of cancer-related pain has potential to enhance understanding of pain risk factors, measurement and classifications of pain intensity, and means to improve pain management. Cancer pain prevalence estimates have varied widely, ranging from 14% to 100%. Chronic or recurrent pain affects about 30% of all patients with

cancer, and about 60 to 90% of patients with advanced cancer.[1,2] There is a need to study patients' experiences of pain over the course of disease using longitudinally-collected, tumor-specific data, as well as to evaluate the effect of risk factors on pain over the course of cancer treatment. The Agency for Healthcare Research and Quality (AHRQ) evidence-based reports focusing on cancer pain published in 2001 and 2002 cite the need for more comprehensive description of the patient's experience of pain over the course of treatment or continuum of care.

The AHRQ synthesis of studies of influences on cancer pain suggest that age, gender, tumor type, genetics, psychosocial context, and cultural factors (e.g., societal norms) affect both the experience of pain, and analgesic efficacy. Specific studies of risk factors for pain have found that among patients with breast cancer, younger patients are at higher risk for post-treatment pain.[3,4] Minority patients have been found consistently to be at greater risk of not only mortality from disease as compared with Caucasian patients,[5,6] but also worse pain outcomes, and specifically undertreated cancer pain.[7-10] A recent study of survival in the Carolina Breast Cancer Study found that African-American women were genetically at higher risk than Caucasian women for a faster-progressing form of breast cancer.[5] This finding could mean greater potential for pain risks due to faster disease progression among African-American women with breast cancer. Studies (in addition to the evidence-based reviews discussed) have cited the need for future study to identify specific risk factors and further investigate those factors identified to date.[11,12]

Pain outcomes research and clinical practice often depend on classifying pain into severity categories according to cutpoints on a 0-10 numeric rating scale.[13,14] Cutpoints are used to drive treatment decisions, develop practice guidelines, and determine effectiveness of

interventions. The World Health Organization (WHO) pain ladder is a treatment guideline that involves the tiered categorization of pain as mild, moderate, or severe; such tiered categorizations rely on specific numeric cutpoints on numeric pain rating scales as guides to clinicians to help distinguish levels of pain intensity on the scale.[13] Where the cutoff point is set for severe pain also informs descriptive epidemiology, including etiological reports on longitudinal cancer pain, as well as prevalence estimates at a given time point. In 1991, Serlin and colleagues report a study in metastatic cancer patients, using analysis of variance methods to anchor the BPI severity scale using the BPI interference scale. They found optimal cutpoints that formed 3 distinct levels of pain severity on 0-10 numeric rating scale (NRS): 1-4: mild, 5-6: moderate, 7-10: severe,[15] and discuss a non-linear relationship between the BPI severity and interference scales. Paul and colleagues[14] also derived cutpoints using other patient-reported outcomes measures to anchor the BPI severity scale. Instead of the 7 cutpoint to designate severe pain, they found that the 7 cutpoint signified moderate pain, and the 8 cutpoint designated severe pain.[14] To date, all efforts to categorize pain intensity categories have compared cutpoints with each other and with external anchors or measures indicative of disease states.[13-16] In order to optimize the use of pain scales in research and practice, further investigation is needed to compare and categorize BPI cutpoints.

This study assesses pain hazards over time among women with metastatic breast cancer, identifying sets of clinical and demographic explanatory variables predictive of greater hazards for pain intensity over 51 weeks. We compare these sets of predictors in univariate and multivariate models using different intensity cutpoints 3 through 7 on the BPI severity and interference 0-10 subscales. In addition, we compare all models to explore the

relationship between the pain severity and interference BPI subscales. Our goal was to provide information to inform clinical practice, especially with regards to how the BPI is used to assess, categorize, and treat severe pain in metastatic breast cancer.

2. Methods

For the entire sample of women with metastatic breast cancer, we conducted Cox proportional hazards analyses for reaching different thresholds of pain on the BPI severity and interference scales over time, comparing which sets of clinical and demographic baseline predictors affect time to first reaching different thresholds of pain as defined by cutpoints on the 0 – 10 severity and interference scales. Reaching the intensity cutpoints of 3, 4, 5, 6, and 7 or above on each scale were the outcomes of interest in predictive modeling to analyze each cutpoint separately, then all cutpoints together, exploring interactions between covariates and cutpoints. We chose this range of cutpoints since the values of 0, 1, 2, as well as 8, 9, and 10 on the 0-10 scales are consistently indicative of only the best or worst outcomes; the values of 3-7 on the BPI scales warrant closer attention in analyses, as this range of values is used to establish categories of pain such as mild, moderate, or severe. The results of the clinical trial treatment comparisons are reported elsewhere;[17] comparisons between the treatment arms were not a part of the present study.

a. Patients and procedures

This study was a secondary analysis of existing data from a clinical trial (Novartis protocol 4244603010). Informed consent was obtained from each patient in the original trial, and the multicenter trial was carried out under approval from each institution's ethical review board, in accordance with applicable laws in each country and the Declaration of Helsinki.

The present study was conducted under approval from the University of North Carolina at Chapel Hill Institutional Review Board.

The original clinical trial assessed patient outcomes over 51 weeks using the BPI[18] to measure pain among 1124 patients with metastatic breast cancer. Saad et al.[19] provide a full report of the primary analyses of the double-blind, multicenter clinical trial, the purpose of which was to compare two bisphosphonate drugs, intravenous zoledronic acid [4 or 8 mg] versus intravenous pamidronate disodium [90 mg], as an adjunct to standard therapies, in the treatment of multiple myeloma and breast cancer patients with cancer-related bone lesions. No placebo arm was used. The original intent-to-treat study population consisted of men and women with stage III multiple myeloma (n = 510) or stage IV breast cancer with at least 1 lytic or mixed bone metastasis (n = 1130). For the purpose of the present analysis, we excluded 6 men, limiting the sample to women with breast cancer (n = 1124). The trial was conducted at 207 centers in the following countries (grouping identified in parentheses): Canada and the United States (North America); Argentina, Brazil, Chile, Peru, and Uruguay (South America); Austria, Belgium, the Czech Republic, France, Germany, Ireland, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, and the United Kingdom (Europe); and Australia, Israel, New Zealand, and South Africa (other). The first patient was recruited on October 16, 1998, and the last assessment was completed on the last patient on January 12, 2001.

b. Assessment of outcomes: pain severity and interference

Patients completed the Brief Pain Inventory questionnaire at baseline, months 1 and 2, and every other month thereafter up to Week 51. The BPI was administered in person prior to the patient being interviewed by the physician or receiving study medication. The BPI

measure consists of several parts, but this study used only the pain severity and interference items. Severity is measured as: average pain, pain right now, worst pain, and least pain, all four of which are answered on a 0-10 scale, with 0 = "no pain" and 10 = "worst pain imaginable". The severity composite score was calculated as the arithmetic mean of the 4 severity items when none of the 4 were missing. The BPI includes a 7-item pain Interference scale, which consists of the same 0-10 response scale to the question: "describe how, during the last 7 days, pain has interfered with your: 1) general activity, 2) mood, 3) walking ability, 4) normal work (includes both work outside the home and housework), 5) relations with other people, 6) sleep, and 7) enjoyment of life. The arithmetic mean of the 7 interference items was used to measure pain interference. This mean was calculated only when at least 4 of the 7 individual items were not missing at a given assessment.

In general, numeric rating scales (NRS) for pain severity such as the BPI have been demonstrated to be valid and sensitive to change.[20] According to the American Pain Society Clinical Practice Guideline for the Management of Cancer Pain in Adults and Children,[21] NRS measures are among the most common, valid, and reliable measures used to assess cancer pain severity, and are preferred by patients over visual analogue scale (VAS) measures. The BPI has been administered and assessed for validity in several languages including Spanish, French, Japanese, Chinese, Italian, Hindi, German, Greek, and Vietnamese.[22-28]

c. Assessment of predictors: clinical and demographic covariates

In addition to the pain assessments, subjects were asked to provide demographic, clinical, and other outcomes information through interviews, written questionnaires, physical examinations, and completion of the clinical case report form and other original clinical trial

source documents in accordance with the study protocol. For our analyses, we grouped all the patients together, comparing how pain hazards differed in relation to baseline clinical and demographic characteristics. These characteristics include performance status (measured by Eastern Cooperative Oncology Group [ECOG] performance status [1 = active (ECOG status of 0 or 1), 0 = restricted (ECOG status of 2 or more)]), age, education (1 = college degree, 0 = no college degree), employment status (1 = full-time, 0 = other), geographic region (North America, South America, Europe, or Other, all defined in the previous section), antineoplastic therapy on study entry (chemotherapy plus hormonal therapy vs. hormonal therapy only), previous skeletal-related event, or SRE (0 = no, 1 = yes), and time from documented initial bone metastasis to randomization. SRE refers to a set of complications defined in the trial as experiencing one or more of the following: pathologic fractures, spinal cord compression with vertebral compression fracture, the need for surgery to treat or prevent pathologic fractures or spinal cord compression, or the need for radiation to bone.[29]

d. Statistical analysis

We conducted the analyses using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) and SAS-callable SUDAAN Release 9.0 (Research Triangle Institute, Research Triangle Park, NC, USA). Analyses were conducted on the intent-to-treat sample, which included all female breast cancer patients who had participated in the trial.

We examined descriptive data on demographic characteristics and clinical variables at the time of study enrollment. We assessed the extent of missing data for the pain outcome variables at each study visit at every relevant study visit. Some patients were missing pain outcome data at every visit. The present analyses excluded these patients (n = 73 completely missing for severity, leaving an analysis sample of n = 1051 for the severity scale, and n = 77

completely missing for interference, leaving an analysis sample of n = 1047 for the interference scale). We used Cox proportional hazards models to assess the relationship of baseline predictors with time to reach pain cutpoints 3, 4, 5, 6, or 7 on the 0-10 severity and interference scales. We examined these cutpoints separately in the univariate analyses, and simultaneously in the multivariate analyses.

Time-to-event was calculated as the number of days from trial enrollment until the patient reported reaching a given severity cutpoint (3, 4, 5, 6, or 7) on the BPI. For each cutpoint, those who never reached that cutpoint as of trial completion (51 weeks, or 357 days, post-randomization) or dropped out of the study were classified as censored. For censored patients, the event indicator variable was set to 0, and time at risk was the time from their enrollment date to trial completion or dropout.

We used visual examination of Kaplan-Meier (KM) curves along with the log-rank test statistic to assess the candidacy of each covariate for stepwise univariate modeling. Covariates for which the KM curves did not cross and the log-rank test was significant at a criterion of $\alpha = 0.05$ were considered best candidates as potential explanatory variables for inclusion in the Cox proportional hazards models. Continuous covariates were dichotomized at the mean if normally distributed, or at the median if non-normally distributed, for the purposes of the KM curve analysis and to be used as dichotomous predictors. Age was distributed normally, and dichotomized for the multivariate analyses at its mean of 57.9 (SD ±12.7). The lower age category was 24-57, resulting in age categories of 24-57 and 58-95 years. Days from bone metastasis to randomization was non-normally distributed, and dichotomized at its median of 104 days (interquartile range = 36 to 475 days).

Time-to-event model building techniques were conducted with the goal of creating parsimonious predictive models to determine the covariate-adjusted hazards of reaching each cutpoint over time. These techniques relied on the stepwise procedure with model entry specified at 0.25, and staying criteria specified at 0.15. The univariate Cox proportional hazards models are expressed as follows: $h(t \mid \boldsymbol{X}) = h_0(t)e^{\left(\sum_{k=1}^{p}\beta_k X_k\right)}$ where $h(t \mid \boldsymbol{X})$ is the hazard for an individual with covariate set $\boldsymbol{X}$, $h_0(t)$ is the non-specified baseline hazard function (when all $X_k = 0$), p is the number of explanatory variables, and $e^{\left(\sum_{k=1}^{p}\beta_k X_k\right)}$ is a known function.

To analyze the time until first reaching each cutpoint explored (3, 4, 5, 6, and 7 on the 0-10 scale) simultaneously with the same explanatory covariates, we fit multivariate Cox proportional hazards models using PROC SURVIVAL in SUDAAN, which implements a Taylor series variance estimation to account for within-subjects correlation between multiple possible outcomes. The explanatory variables used as baseline predictors were ECOG performance status, age, race, college education, full-time employment, and previous skeletal related event. We chose this set of explanatory variables for the multivariate model because these factors had emerged as most consistently influential across the univariate analyses. In the multivariate model, each patient had several potential outcomes: time to first reaching the score of each cutpoint (3, 4, 5, 6, and 7) or higher on the 0-10 scales. To model these outcomes simultaneously, we fit the Cox proportional hazard model with p covariates as follows: $h_j(t) = h_0(t)e^{\alpha_j + \sum_{k=1}^{p}\beta_{jk}X_{jk}}$ where j = 3, 4, 5, 6 or 7 for the different pain

score cutpoints. This equation applies to any patient *i*. We assume proportional hazards across different outcomes reflected by a constant α_j. β_{jk} can be the same for different outcomes. We used only the baseline assessment of all the clinical and demographic covariates described. Therefore, each covariate was considered time-independent in the models.

These data presented an opportunity to explore the relationship between the BPI intensity composite score and the BPI interference composite score. Both scales are rated numerically on a 0-10 scale, with 10 indicating greatest severity or interference. To explore the relationship of these two subscales, we explored the similarities and differences in how sets of explanatory covariates affected pain severity versus interference outcomes, using the same analyses described above to estimate hazards for pain on each of the two scales.

e. Sensitivity analyses

Censoring deaths versus assigning worst pain score

An overarching issue that affected all the survival analyses was that in the analyses, death may be dealt with either by: 1) censoring, or 2) treating death as an event of the worst possible outcome (severe pain).[30] We conducted a sensitivity analysis to address this issue. For those individuals who died, instead of censoring their observation, we assigned time to reach severity of 7 or higher at the time of death as if death were comparable to a BPI score of 10, and the time of death was the last time for pain assessment. The dropout date was effectively either the last day of enrollment in the trial, or the last day the BPI was administered, whichever was the later of the two. We compared the model results using this technique with those results from conventional censoring.

Missing data methods

The continuous time assumption for survival analysis required assumptions about handling the event indicator and time at risk variables, when pain data were partially missing. In these cases, we implemented the following coding for event indicator and time-to-event variables: if the patient had some BPI data but never reached the outcome, then the dichotomous event indicator variable was set equal to 0. The observation was censored, and total time at risk was set equal to either the total number of days the patient was in the study (Assumption A), or to the number of days from trial enrollment to the date of the preceding non-missing BPI measurement (Assumption B). We conducted a sensitivity analysis to compare results under Assumption A versus Assumption B.

Another missing data handling technique used was to code the full-time employment and college education variables (each of these variables had about 16% missing data at baseline) as three-level categorical variables, with the categories as "yes", "no", or "missing", with "yes" as the referent so that the effect of lower educational attainment or no employment could be assessed. This technique prevents these individuals from being dropped from the models.

3. Results

We assessed the risk of pain severity and interference outcomes among 1,124 women with metastatic breast cancer, whose baseline characteristics are presented in Table 1. The two variables for which more than 1% of patients had missing observations at baseline were education and employment status, which were each missing for approximately 16% of the sample. Only 14% of patients reported being employed full-time at the time of trial

enrollment. This is likely due to the fact that all patients in the trial had metastatic disease at enrollment.

Of the 438 patients (39% of the original 1124 enrolled) who did not complete visit 19, 132 patients (30%) discontinued the study due to adverse events. Twenty-six percent (n = 113) died. For the entire trial population, approximately 52% of adverse events experienced were bone pain, making it the most frequent type of adverse event. Implications of this fact with regards to the proportional hazards assumption are addressed in the sensitivity analysis. Table 2 shows the study population remaining at each scheduled BPI assessment (visits 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, and 19) and the proportion of participants completing the BPI severity and interference assessments. Of those women enrolled in the trial at any given visit, the proportion who had completed BPI assessments was consistently no less than 82%. Data were excluded for visits at which the BPI was not scheduled. Patients were excluded from the analyses if they had BPI scores missing at all assessments (73 patients were excluded from the original 1,124 due to missing severity data, and 77 were excluded due to missing interference data). Of the 438 patients (39% of the original 1124 enrolled) who did not complete visit 19, 132 patients (30%) discontinued the study due to adverse events, and 113 patients (26%) discontinued due to death. Additional details regarding patient disposition for the overall clinical trial are reported by Rosen et al.[17]

Figure 1 shows the Kaplan-Meier curves for time to first reach BPI severity cutpoints 3, 4, 5, 6, and 7. These curves are based on all subjects with at least one BPI severity score (n = 1051). The time until first reaching a given pain score increases as the pain score outcome increases; thus, over the observation period patients overall were more likely to reach a score

of 3 or above than to reach a score of 4 or above, and successively higher pain scores were less likely.

Results of the univariate (per-cutpoint) Cox proportional hazards analyses, shown in Tables 3 and 4, corroborated assessments of the KM curves and log-rank tests in identifying restricted ECOG performance status and non-Caucasian race as most consistently predictive of worse pain outcomes across cutpoints for both severity and interference outcomes. Previous SRE was a predictor in each univariate model by cutpoint, except for 7 on the severity scale, and for all cutpoints except for 6 on the interference scale. Continuous age in decades was a predictor for only the 7 cutpoint on the severity scale, but was a predictor for all cutpoints on the interference scale. College education was a predictor only for the 6 cutpoint on the severity scale. The number of days from bone metastasis to randomization (categorical coding, dichotomous at median = 104 days) was not found to be predictive in any univariate model, nor were geographic region or chemotherapy adjunct to hormonal therapy at baseline. ECOG performance status, experience of a previous SRE, race, age dichotomous at the mean of 57, education, and employment were included as predictors in the multivariate (all-cutpoint) proportional hazards models for pain severity and interference. Employment status was not found to be predictive in any univariate model, but was retained for the multivariate model because the log-rank test statistics were statistically significant at $\alpha = 0.05$ for all cutpoints. As a demographic characteristic, employment status also has *a priori* value as a potential predictor in the multivariate models because employment at baseline signifies better health.

For the multivariate model of pain severity outcomes, a proportional hazards model was fit to assess hazards simultaneously for time to first occurrence of a 3, 4, 5, 6, or 7 on each of

the 0-10 severity and interference scales, with employment status and college education as 3-level categorical variables, and age dichotomous at 57 years or less versus > 57. Table 5 displays the model parameters for the multivariate model for all cutpoints. Factors that were associated with higher hazard of reaching any of the 3-7 cutpoints on the severity scale were: restricted baseline ECOG status (HR = 1.70, 95% confidence interval [CI] =1.41 - 2.06), previous skeletal related event (SRE) (HR = 1.23, 95% CI =1.06 – 1.44), and not employed full-time (HR = 1.33, 95% CI =1.06 – 1.67). Age and college education did not appear to have a significant association with pain severity (HR = 1.12, 95% CI =0.97 – 1.31, and HR = 1.18, 95% CI =0.99 – 1.41, respectively). Race was found to modify the effect of reaching any cutpoint 3-7; a race by cutpoint interaction term was found statistically significant (Wald *F* test p-value = 0.033) and included in the multivariate model. Hazard ratios comparing Caucasian race with non-Caucasian race for first occurrence of pain severity differed according to cutpoint. For example, compared with Caucasian race, non-Caucasian race was associated with 2.29 times the hazard of reaching severity cutpoint 7 versus 1.38 for cutpoint 3, all other covariates held constant. This contrast may be calculated either using the HRs as follows: $HR_{\text{non-Caucasian}} * HR_{\text{Cutpoint 7}} = 1.38 * 1.66$, or using the ß coefficients (not shown in tables) estimated from the model as follows:

$$e^{[\beta_{\text{Non-caucasian}}(1\text{-}0) + \beta_{\text{Cutpoint 7}}(1\text{-}1) + \beta_{\text{Non-caucasian * cutpoint 7}}(1\text{-}0)]} = e^{[0.32 + 0.51]} = 2.29$$

Other contrasts can be computed similarly.

Table 6 displays the model parameters for the multivariate Cox proportional hazards model with time to first pain interference cutpoints as the correlated outcomes. Factors that were associated with higher hazard of reaching any cutpoint on the interference scale were: non-Caucasian race (HR = 1.40, 95% CI =1.13 – 1.74), previous SRE (HR = 1.20, 95% CI

=1.03 – 1.40), younger age (57 years or less) (HR = 1.39, 95% CI =1.19 – 1.62), and not employed full-time (HR = 1.45, 95% CI =1.15 – 1.83). The 95% CI for college education did not exclude the null value (HR = 1.08, 95% CI =0.91 – 1.28). For the interference outcome, baseline ECOG performance status was found to modify the effect of reaching any cutpoint 3-7; the ECOG performance status by cutpoint interaction term was found statistically significant (Wald *F* test p-value = 0.004) and included in the multivariate model. For the interference scale, hazard ratios comparing restricted versus active Eastern Cooperative Oncology Group (ECOG) performance status for first occurrence of pain interference differed according to cutpoint. For example, compared with active baseline ECOG status, restricted baseline ECOG status was associated with 2.97 times the hazard of reaching interference cutpoint 7 versus 2.00 for cutpoint 3, all other covariates held constant (this and other contrasts in the presence of the interaction term may be calculated as described above for the severity outcome).

The factors found to be predictive of greater hazards for both the severity and interference outcomes were non-Caucasian race, restricted baseline ECOG status, previous SRE, and not being employed full time. Younger age was predictive of higher hazards only in the interference scale. Hazards of reaching higher pain cutpoints differed by race on the severity scale, and by ECOG status on the interference scale. All of the findings were found to be robust in direction, magnitude, and statistical significance under sensitivity analyses varying handling of deaths and missing data.

Table 6. (MS1: Table 1). Baseline patient characteristics and missing data (N = 1124).

Characteristic	Values[A]	Number of patients with values missing at baseline (%)
Age in years, mean ± SD	57.5 ± 12.6	0 (0)
Female	1124 (100)	0 (0)
Race[B]		0 (0)
Caucasian	991 (88)	
Black	64 (6)	
Oriental	17 (2)	
Other	52 (5)	
College education	281 (25)	186 (17)
Employed full-time	157 (14)	182 (16)
Geographic region[C]		0 (0)
North America	773 (69)	
Europe	217 (19)	
South America	39 (3)	
Other	95 (8)	
Baseline ECOG performance status		4 (0.4)
Active (0 or 1), recoded as 1	952 (85)	
Restricted (≥2), recoded as 0	168 (15)	
Antineoplastic therapy (trial stratification variable)		0 (0)

Characteristic	Values[A]	Number of patients with values missing at baseline (%)
Chemotherapy	525 (47)	
Hormonal therapy	599 (53)	
Experienced previous skeletal related event	677 (60)	3 (0.3)
Time from first bone metastasis to randomization, days	157 (14)	3 (0.3)
Mean ± SD	406 ± 744	
Median	108	

[A]Values are expressed as number (percentage) unless otherwise indicated.
[B]Race categories are reported as they were asked in the clinical trial case report form. Race variable was recoded to Caucasian/non-Caucasian for the present analyses.
[C]Variable was recoded to North America/Other for present analyses.
Some totals do not add up to 100% due to rounding.
SD = Standard deviation
ECOG = Eastern Cooperative Oncology Group

Table 7. (MS1: Table 2). Study population and Brief Pain Inventory (BPI) completion at each scheduled assessment

Visit	Study Population [A]	Completeness of BPI Composite Scores			
		Severity Score		Interference Score	
		n (% of pts. in trial at visit *i*) [B]	(% of starting N)	n (% of pts. in trial at visit *i*) [B]	(% of starting N)
Visit 2	1124 (100)	1024 (91)	(91)	1029 (92)	(92)
Visit 3	1117 (99)	975 (87)	(87)	972 (87)	(86)
Visit 4	1073 (95)	950 (89)	(85)	953 (89)	(85)
Visit 6	1019 (91)	898 (88)	(80)	906 (89)	(81)
Visit 8	942 (84)	806 (86)	(72)	807 (86)	(72)
Visit 10	896 (80)	794 (89)	(71)	798 (89)	(71)
Visit 12	812 (72)	675 (83)	(60)	675 (83)	(60)
Visit 14	784 (70)	673 (86)	(60)	681 (87)	(61)
Visit 16	706 (63)	598 (85)	(53)	599 (85)	(53)
Visit 18	672 (60)	551 (82)	(49)	549 (82)	(49)
Visit 19	686 (61)	584 (85)	(52)	583 (85)	(52)

[A]Indicates the number (percent) of patients remaining in the study at each scheduled BPI assessment visit.

[B]Indicates number of patients at each BPI assessment for whom BPI Composite Scores could be calculated.

Table 8. (MS1: Table 3). Hazard ratios for pain severity: per-cutpoint univariate Cox proportional hazards models, continuous time assumption.

Model: Severity Cutpoint	Parameter	Estimate	SE	HR (e^{β_k})	95% CI for HR	Resid. χ^2 test statistic (df), p-value
3	Active baseline ECOG	-0.39	0.10	0.68	0.56 - 0.82	0.92 (6), 0.988
	Previous SRE	0.15	0.07	1.16	1.01 - 1.35	
	Caucasian race	-0.26	0.11	0.77	0.63 - 0.95	
4	Active baseline ECOG	-0.53	0.10	0.59	0.48 - 0.72	1.18 (6), 0.978
	Previous SRE	0.16	0.08	1.18	1.00 - 1.39	
	Caucasian race	-0.34	0.11	0.72	0.57 - 0.90	
5	Active baseline ECOG	-0.50	0.12	0.60	0.48 - 0.77	2.58 (6), 0.860
	Previous SRE	0.20	0.10	1.22	1.01 - 1.48	
	Caucasian race	-0.52	0.13	0.59	0.46 - 0.76	
6	Active baseline ECOG	-0.46	0.15	0.63	0.47 - 0.85	0.97 (5), 0.965
	College education[A]	0.003	0.002	1.003	0.999 - 1.006	
	Previous SRE	0.39	0.13	1.48	1.15 - 1.89	
	Caucasian race	-0.68	0.15	0.50	0.38 - 0.68	
7	Active baseline ECOG	-0.62	0.19	0.54	0.37 - 0.78	3.73 (6), 0.713
	Caucasian race	-0.86	0.19	0.42	0.29 - 0.62	
	Age in decades	0.11	0.06	1.12	0.99 - 1.26	

Note: ECOG = Eastern Cooperative Oncology Group performance status. SRE = Skeletal related event.

[A]Values for this line are reported to three decimal places to avoid rounding to 0.00.

Table 9. (MS1: Table 4). Hazard ratios for pain interference: per-cutpoint univariate Cox proportional hazards models, continuous time assumption)

Model: Interference Cutpoint	Parameter	Estimate	SE	HR (e^{β_k})	95% CI for HR	Resid χ^2 test statistic (df), p-value
3	Active baseline ECOG	-0.47	0.10	0.62	0.51 - 0.76	1.04 (5), 0.959
	Caucasian race	-0.20	0.11	0.82	0.66 - 1.02	
	Previous SRE	0.16	0.08	1.18	1.01 - 1.37	
	Age in decades	-0.05	0.03	0.95	0.90 - 1.01	
4	Active baseline ECOG	-0.61	0.10	0.54	0.44 - 0.66	1.76 (5), 0.881
	Caucasian race	-0.19	0.12	0.83	0.66 - 1.04	
	Previous SRE	0.15	0.08	1.17	0.99 - 1.37	
	Age in decades	-0.07	0.03	0.93	0.87 – 0.99	
5	Active baseline ECOG	-0.76	0.11	0.47	0.38 - 0.58	2.55 (5), 0.769
	Caucasian race	-0.25	0.13	0.78	0.61 - 1.00	
	Previous SRE	0.14	0.09	1.15	0.96 - 1.37	
	Age in decades	-0.08	0.03	0.92	0.86 - 0.98	
6	Active baseline ECOG	-0.90	0.12	0.41	0.32 - 0.51	1.88 (6), 0.931
	Caucasian race	-0.42	0.14	0.66	0.51 - 0.86	
	Age in decades	-0.10	0.04	0.90	0.84 - 0.97	
7	Active baseline ECOG	-1.06	0.14	0.35	0.27 - 0.45	1.73 (5), 0.885
	Caucasian race	-0.50	0.16	0.61	0.44 - 0.83	
	Previous SRE	0.23	0.13	1.25	0.98 - 1.61	
	Age in decades	-0.13	0.05	0.88	0.80 – 0.96	

Note: ECOG = Eastern Cooperative Oncology Group performance status. SRE = Skeletal related event.

Table 10 (MS1: Table 5). Multivariate model: effect of explanatory variables on hazards for reaching pain outcomes (BPI severity scale cutpoints 3, 4, 5, 6, or 7).

Independent Variables and Effects	Hazards Ratio	Lower 95% Limit	Upper 95% Limit
Cutpoint			
7	0.10	0.09	0.12
6	0.21	0.18	0.23
5	0.38	0.35	0.41
4	0.64	0.60	0.67
3	1.00	-	-
Restricted ECOG performance status	1.70	1.41	2.06
Previous skeletal related event	1.23	1.06	1.44
Age 57 years or less	1.12	0.97	1.31
Less than College education	1.18	0.99	1.41
Education missing	1.05	0.55	1.97
College education	1.00	-	-
Not Employed full-time	1.33	1.06	1.67
Employment missing	1.43	0.72	2.86
Employed full-time	1.00	-	-

Independent Variables and Effects	Hazards Ratio	Lower 95% Limit	Upper 95% Limit
Cutpoint * Race interaction term			
7 * non-Caucasian	2.29	1.58	3.33
6 * non-Caucasian	1.99	1.48	2.66
5 * non-Caucasian	1.76	1.37	2.26
4 * non-Caucasian	1.46	1.16	1.84
3 * non-Caucasian	1.38	1.12	1.70
Referent[A]	1.00	-	-

Note: ECOG = Eastern Cooperative Oncology Group performance status. Referent categories are displayed only for variables with more than two levels.

[A]The referent categories for the interaction term were {3, 4, 5, 6, or 7} or Caucasian.

Table 11 (MS1: Table 6). Multivariate model: effect of explanatory variables on hazards for reaching pain outcomes (BPI interference scale cutpoints 3, 4, 5, 6, or 7).

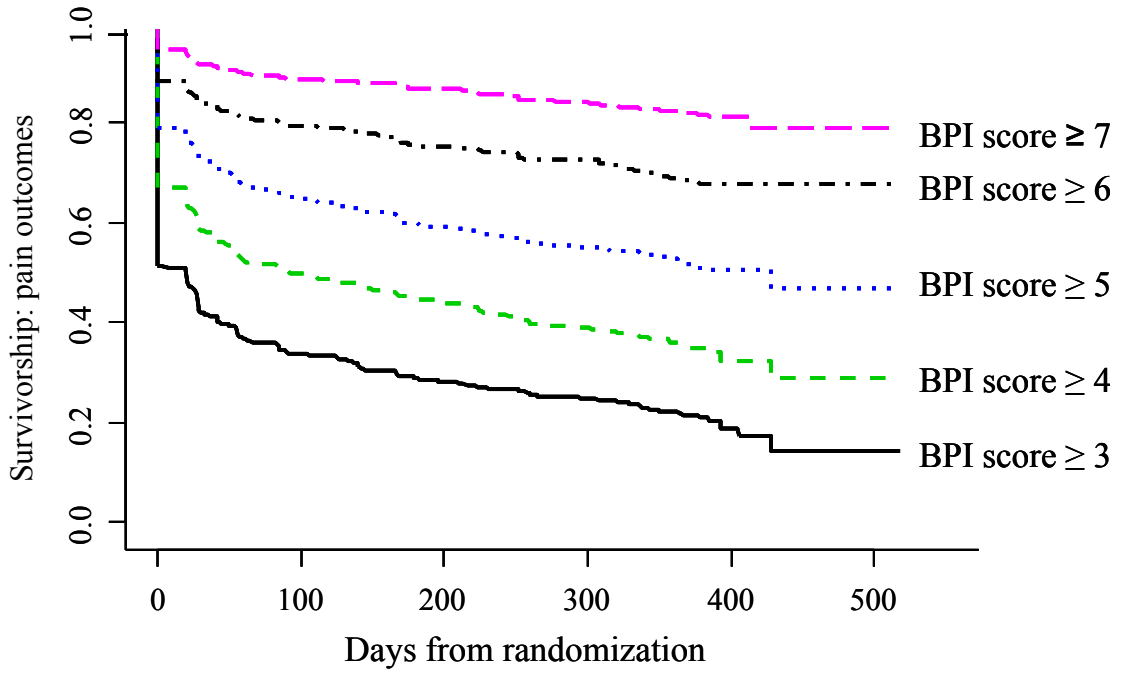
Independent Variables and Effects	Hazards Ratio	Lower 95% Limit	Upper 95% Limit
Cutpoint			
7	0.22	0.19	0.25
6	0.37	0.33	0.40
5	0.54	0.51	0.58
4	0.75	0.71	0.78
3	1.00	-	-
Previous skeletal related event	1.20	1.03	1.40
Non-Caucasian race	1.40	1.13	1.74
Age 57 years or less	1.39	1.19	1.62
Less than College education	1.08	0.91	1.28
Education missing	0.76	0.35	1.65
College education	1.00	-	-
Not Employed full-time	1.45	1.15	1.83
Employment missing	1.78	0.78	4.06
Employed full-time	1.00	-	-

Independent Variables and Effects	Hazards Ratio	Lower 95% Limit	Upper 95% Limit
Cutpoint * Restricted ECOG performance status interaction term			
7 * Restricted ECOG	2.96	2.28	3.85
6 * Restricted ECOG	2.52	1.98	3.20
5 * Restricted ECOG	2.51	2.01	3.13
4 * Restricted ECOG	2.16	1.77	2.65
3 * Restricted ECOG	2.00	1.66	2.42
Referent[A]	1.00	-	-

Note: ECOG = Eastern Cooperative Oncology Group performance status. Referent categories are displayed only for variables with more than two levels.

[A]The referent categories for the interaction term were {3, 4, 5, 6, or 7} or Unrestricted ECOG status.

Figure 20. (MS1: Figure 1). Time to first reach BPI severity cutpoints 3, 4, 5, 6, and 7, unstratified results for entire sample.



4. Discussion

The present study set out to assess risks of reaching different pain severity and interference thresholds over 51 weeks among a sample of women with metastatic breast cancer, to investigate a set of baseline clinical and demographic factors as risk factors for first occurrence of reaching cutpoints 3, 4, 5, 6, and 7 on 0-10 numeric rating scales of the BPI, and to help understand the value of various cutpoints for categorization of pain severity. Our analyses identified the following baseline clinical and demographic factors to be associated with greater hazards of experiencing both pain severity and interference over the course of the observation period: non-Caucasian race, restricted/inactive baseline ECOG performance status, age 57 years or less, not employed full-time, and having experienced a previous skeletal related event (defined as any of the following events: pathologic fractures, spinal cord compression with vertebral compression fracture, the need for surgery to treat or prevent pathologic fractures or spinal cord compression, or the need for radiation to bone).

Our findings that age and race were important predictors of pain severity and interference with daily living over time are consistent with other risk-factor studies and clinical practice guidelines,[31] including reports that among patients with breast cancer, younger patients are at higher risk for post-treatment pain,[3,4] and that minority patients have been found consistently to be at greater risk of worse pain outcomes and of undertreated cancer pain specifically.[7-10] Similarly, the ECOG performance status and employment variables represent levels of activity versus restriction/impairment at baseline, an important construct that has emerged in past research as a predictor for pain and other health-related quality of life outcomes.[32,33] Oncologist-assessed ECOG performance status has been shown to have important prognostic value in predicting, with distinct discrimination at each level of the ECOG scale, survival

outcomes among patients with non-small cell lung cancer.[34] In confirming these characteristics as risk factors over time among patients with metastatic breast cancer, our findings inform individualized prognoses for pain outcomes according to baseline patient attributes. Using this information, earlier intervention and more aggressive pain management strategies can be tailored to these personalized prognoses with the goal of delaying the first occurrence of higher pain scores among those at greater risk for severe pain and pain interference in daily activities.

On the severity scale, race affected time to occurrence of reaching each cutpoint such that non-Caucasians were found to have greater hazards than Caucasians for experiencing pain scores of 5, 6, or 7. Paul and colleagues stated that they could not determine in an all-Caucasian sample whether cutpoints vary based on cultural or ethnic differences in how individuals interpret pain severity ratings.[14] The findings of the present study do provide evidence that cutpoints vary according to racial/ethnic categories, but do not address specifically the question of whether ethnic differences affect interpretation of pain severity ratings. Potential differences in clinical reporting and treatment of pain affect pain outcomes over the course of cancer. If there are significant differences by race in pain outcomes as reported by the patients, these differences may be due to either inaccurate patient reporting, or differences in actual true levels of pain. Without clear evidence of the former, it seems more conservative to assume that these differences reflect actual disparities in patients' experiences of pain, originating from sources external to the patient.

Our exploration of the relationship between the severity and interference subscales of the BPI showed that baseline clinical and demographic risk factors were largely similar between the two scales in their associations with pain hazards over time. However, while race appears

to influence time to first event of reaching different severity cutpoints, baseline ECOG performance status influenced time to first occurrence of reaching different cutpoints on the interference scale. The two scales measure distinct underlying constructs; interpretations of results obtained with these BPI subscales should take into account two baseline traits as modifiers of the effects measured by these subscales of the BPI: race for the severity subscale, and performance status for the interference subscale.

In the univariate analyses, the constellation of risk factors was relatively consistent over the range of cutpoints from 3 to 7 for both the severity and interference scales, with race a significant predictor in all individual cutpoint (univariate) models. The findings from the multivariate pain severity analysis indicate that non-Caucasian women were at greater hazard of reaching higher pain severity scores earlier than their Caucasian counterparts. The interaction term for this hazard was significant at values of 5 and higher on the BPI. Given the potential risks of undertreated pain, these findings should aid in future research to evaluate the role of cutpoints in making pain treatment decisions, aimed to delay or prevent worse outcomes among those patients at greatest risk over time.

The large trial population of 1,124 patients may be considered a strength of the present study, assuming minimal impact of potential bias related to the trial sampling methods on this sample's representativeness of women with metastatic breast cancer. Early research on how clinical trial participants differ from non-participants suggests that trial participants have less mortality than non-participants.[35] In their 2004 study of cancer clinical trial participation, Murthy and colleagues found that younger and minority patients were less likely than their counterparts to participate in cancer clinical trials.[36] However, the distribution of race in this study (recorded as "Black" for 5.7% of the sample) appears close to the distribution of race

among prevalent first malignant breast cancer cases in 2002 in the U.S. (Black = 7.4% of total cases) estimated by Surveillance, Epidemiology and End Results (SEER).[37] With regards to age, women aged 57 years or less composed approximately half the trial population, while 20% of prevalent breast cancer cases were aged 54 or lower in 2002 U.S. estimates (27-year limited-duration prevalence, first malignant cancer only).[37] Thus, both the age and race distributions in the present study seem to represent the populations to which we would generalize the findings, although the influence of potential bias with regard to traits affecting pain outcomes cannot be ruled out entirely.

A strength of the clinical trial design was that pain was measured at multiple time points. Because bone pain was the most frequent type of adverse event experienced by patients in this trial, it is realistic to assume that pain would be related to early termination through dropout or death. If this were the case, the censoring distribution would not be independent of the outcome, and the proportional hazards assumption would not be met. However, when we conducted sensitivity analyses varying handling of deaths and missing data, our findings did not change markedly in direction, magnitude, or statistical significance.

A limitation of this study is that although the dataset used contains pain information at multiple assessment times per patient, the pain severity questions were asked over the timeframe of the past seven days (with the exception of "describe your pain right now") and the pain interference questions were asked over the timeframe of the past 24 hours. This means that gaps in information as long as 5 weeks exist in the severity data, and even longer gaps exist in the interference data. The impact of this limitation on the present study is that although we are able to assess pain hazards over time based on the information available, pain severity and/or interference may have increased or decreased during the gaps between

assessments, but these changes not captured. This analysis was also limited by the characteristics of the clinical trial, which was designed to answer research questions about the relative efficacy of two bisphosphonates. The clinical trial itself dictated specific inclusion/exclusion criteria, and which covariates were collected in this sample. Although all patients were given at least standard treatment, the present study lacks more detailed information on analgesic treatments as they varied with time. Such information is useful in understanding fluctuations and changes in pain severity and interference over time.

Future research should collect and model the effects of risk factors upon longitudinal pain outcomes, aided by prospective design to incorporate constellations of clinical and non-clinical factors known to affect pain. In addition to clinical information such as analgesic treatment and guideline adherence, non-clinical factors should be included as well, such as patient medication adherence, patient and physician barriers to effective analgesic treatment (the patient portion of which can be measured through the Patient Barriers Survey[38]), patient-physician communication, psychological, and cultural factors.

Our findings emphasize the need for early intervention and more aggressive pain management strategies tailored to individual patient characteristics, and implemented over the course of treatment. This strategy may differ from modular pain management using the analgesic ladder and the previously defined BPI severity cutpoints. Given that patients with metastatic breast cancer who were non-Caucasian, restricted in performance status, younger, or not employed at baseline were found to have higher hazards as compared with their counterparts for first reaching higher levels of pain sooner, our findings suggest that intervention strategies be targeted to prevent or delay first occurrence of higher-intensity pain among those at greater risk.

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B. Manuscript 2: Factors associated with differential hazards for pain treatment failure among metastatic breast cancer patients

ABSTRACT

Background. A research need has been cited for tumor-specific epidemiologic study of baseline and time-dependent risk factors, especially with regards to racial disparities, for pain experienced over time among patients with cancer. Clinical trials may collect pain data at multiple time points, but often only single time point or percentage-change-from-baseline approaches are implemented. The present study utilized longitudinal data to (a) identify baseline and time-dependent risk factors for time to first occurrence of experiencing a 7 or above (treatment failure) on Brief Pain Inventory 0-10 severity and interference scales; (b) test the hypothesis that racial/ethnic classification would be an important predictor for worse pain outcomes; and (c) explore the relationship between pain severity and interference as measured by the subscales of the BPI.

Methods. We conducted a secondary analysis of existing data from a clinical trial that assessed patient outcomes over at least 51 weeks using the Brief Pain Inventory (BPI) to measure pain among 1124 women with metastatic breast cancer. We fit models to data structured by 80-day intervals to predict hazards of reaching a score of 7 or greater on the (BPI) severity and interference scales over 400 days, assessing race as well as baseline and time-dependent covariates as predictors of pain outcomes.

Results. Caucasian race and active Eastern Cooperative Oncology Group (ECOG) performance status were associated with decreases in log incidence density, and radiation treatment since the last study visit was associated with an increase in log incidence density for both outcomes. The estimated survival rate at the first interval was 0.92 for Caucasian

women versus 0.80 for non-Caucasian women for the severity outcome, and 0.80 for Caucasian women versus 0.70 for non-Caucasian women for the interference outcome. In subsequent intervals, these rates declined similarly for Caucasian and non-Caucasian women, but for both pain outcomes, the cumulative survival rate for Caucasians in the last interval was still higher than the rate for non-Caucasian women in the first interval.

Discussion. Our findings support the hypothesis that non-Caucasian race is a risk factor for worse pain severity and interference, not only cross-sectionally, but also longitudinally among women with metastatic breast cancer. Our findings with regard to restriction/impairment as measured over time by performance status offer longitudinal evidence to confirm that performance status is an important predictor of pain and other health-related quality of life outcomes. Our findings should help to inform individual prognoses and pain management strategies according to patient attributes that are available for assessment over time. Future research should aim to assess pain comprehensively over time in tumor-specific cohorts, and to incorporate data collection designs that specifically target sources of racial disparities.

1. Introduction

Pain, often called the "fifth vital sign", is of particular concern in cancer due to the malignant nature of neoplastic disease, the physiological mechanisms of cancer progression, and the pain-causing potential of cancer treatments and their side effects. It is estimated that chronic or recurrent pain affects about 30% of all patients with cancer, and about 60 to 90% of patients with advanced cancer.[1,2] However, the burden of pain is consistently found to be greater among non-Caucasian versus Caucasian patients in cross-sectional research. Few

studies of cancer pain have examined whether patients' experiences of pain over the course of disease differ by race.

In addition to being at higher risk for breast cancer mortality,[3] non-Caucasian patients with cancer have been found to report greater pain, and to be at risk for having their pain inadequately assessed,[4] managed, and treated.[5] In a 1998 study by the SAGE group,[6] African-American patients (a) reported more daily pain (34% as compared to 25% of white patients), (b) had greater odds of failing to receive any analgesic agent, and (c) were found to have inadequate pain management at higher rates than white patients in outpatient clinics.[6] Such disparities have been further confirmed and discussed in other investigations, which have cited differences in treatment patterns, pain management strategies, and the use of hospice care as potential contributing factors to racial differences.[3,7,8] Sources of pain disparities by minority status are complex, simultaneously involving factors on all levels of health and health care. This study explores race as a risk factor by investigating the hypothesis that pain hazards over time will be higher among non-Caucasian patients with metastatic breast cancer, as compared with their Caucasian counterparts.

Approaches to pain research have comprised observational, experimental, meta-analytic, and measurement/validation designs to explore cancer pain incidence and prevalence, risk factors for pain, the effectiveness of various analgesic interventions, and the construction and testing of algorithms for pain management strategies based on available evidence. Although there is wide consensus that pain is a key dimension of detriments in health-related quality of life, large-scale evidence reviews have identified gaps in research, citing a need for tumor-specific studies of patients' experiences of pain over time, with consideration of how various factors affect longitudinal experiences of pain during the course of treatment.[9,10] A 2004

monograph on the methodology and future directions for epidemiologic research of cancer pain calls for studies that more clearly characterize the pain experience over the cancer trajectory.[11] Most pain prevalence investigations have involved only cross-sectional data collected at one point in time.[11] In clinical trials, pain data may be collected at multiple time points, but the trial statistical analyses are often limited to the use of one measurement at a single time point or percentage-change-from-baseline approaches[12] (in which the analysis covers data collected at only two time points: the first and last pain assessments, no matter how many times pain was assessed during the trial). The approaches described do not optimize understanding that can be gained from using time-to-event methods for analyzing data collected at multiple visits.

The study of longitudinal pain outcomes must take into account established and potential risk factors for pain that have been found in previous studies. Studies of risk factors for pain have found that among patients with breast cancer, younger patients are at higher risk for post-treatment pain.[13,14] In addition, tumor type, genetics, psychosocial context, and culture have been found to affect pain and analgesic efficacy.[15]

In their measure validation study of the Brief Pain Inventory (BPI),[16] Serlin and colleagues used the BPI interference scale to anchor cutpoints on the BPI severity scale for pain intensity levels.[17] They found optimal cutpoints that form 3 distinct levels of pain severity on 0-10 numeric rating scale (NRS). 1-4: mild, 5-6: moderate, 7-10: severe. Serlin and colleagues also found non-linear relationship between the BPI severity and interference scales. The findings of a 2005 study by Paul and colleagues[18] in outpatient oncology patients with metastases confirmed the previous finding of a non-linear relationship between cancer pain severity and interference. These two outcome measures are often administered together

in clinical trials, and are of importance in describing pain as a patient-reported outcome. Further investigation of the relationship between the scales can help us gain a more complete understanding of the impact of cancer pain.

In addition to its importance for measure validation studies, the cutpoint of 7 on the BPI is also of clinical interest. Designations of severity based on cutpoints have been used to establish clinically meaningful changes (used to measure therapeutic effectiveness), as well as in the creation of clinical practice guidelines and in the analyses for numerous cross-sectional studies of pain intensity in different populations. A patient-reported pain score of 7 or above is often a red flag to clinicians that a change in pain management is necessary,[19] because treatment to that point has failed to prevent severe pain. Thus, a pain score of 7 may be termed a treatment failure.

The aims of this study were (a) to identify baseline and time-dependent factors associated with time to first occurrence of experiencing a 7 or above on scales measuring pain severity and pain interference with daily function; (b) to test the hypothesis that racial/ethnic classification would be an important predictor for worse pain outcomes; and (c) to explore the relationship between pain severity and interference as measured by the 0-10 scales of the BPI.

2. Methods

    a. Patients and procedures

Our study was conducted under approval from the University of North Carolina at Chapel Hill Institutional Review Board. We analyzed data from participants in a clinical trial (Novartis protocol 4244603010). Informed consent was obtained from each patient in the original trial, and the multicenter trial was carried out under approval from each institution's

ethical review board, in accordance with applicable laws in each country and the Declaration of Helsinki. The trial assessed patient outcomes over 51 weeks using the BPI[16] to measure pain among 1124 patients with metastatic breast cancer. Saad et al.[20] provide a full report of the primary analyses of the double-blind, multicenter clinical trial, the purpose of which was to compare two bisphosphonate drugs, intravenous zoledronic acid [4 or 8 mg] versus intravenous pamidronate disodium [90 mg], as an adjunct to standard therapies, in the treatment of multiple myeloma and breast cancer patients with cancer-related bone lesions. No placebo arm was used. The intent-to-treat study population consisted of men and women with stage III multiple myeloma (n = 510) or stage IV breast cancer with ≥ 1 lytic or mixed bone metastasis (n = 1130). For the purpose of the present analysis, we limited the sample to women with breast cancer (n = 1124). The sample was stratified at enrollment into two categories: (1) patients with breast cancer undergoing chemotherapy or breast cancer patients undergoing both chemotherapy *and* hormonal therapy, versus (2) patients with breast cancer undergoing first-line or second-line hormonal therapy without chemotherapy. These stratification categories were used as covariates in the present study. The clinical trial was conducted at 207 centers in the following countries (grouping identified in parentheses): Canada and the United States (North America); Argentina, Brazil, Chile, Peru, and Uruguay (South America); Austria, Belgium, the Czech Republic, France, Germany, Ireland, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, and the United Kingdom (Europe); and Australia, Israel, New Zealand, and South Africa (other). The first patient was recruited on October 16, 1998, and the last measure was completed on the last patient on January 12, 2001.

b. Assessment of outcomes: pain severity and interference

Patients completed the Brief Pain Inventory questionnaire at baseline, months 1 and 2, and every other month thereafter up to month 13 (Week 51). The BPI was administered in person before the patient was interviewed by the physician or received study medication. The Brief Pain Inventory (BPI) measure consists of several parts, but this study uses only the pain severity and interference items. Severity is measured as: average pain, pain right now, worst pain, and least pain, all four of which are answered on a 0-10 scale, with 0 = "no pain" and 10 = "worst pain imaginable". The "worst pain" or the arithmetic mean of the 4 severity items can be used as measures of pain severity. For the present study, at the advisement of the BPI instrument's creators, we use the arithmetic mean of the 4 severity items rather than the "worst pain" score alone. The BPI includes a 7-item pain Interference scale, which consists of the same 0-10 response scale to the question: "describe how, during the last 7 days, pain has interfered with your: 1) general activity, 2) mood, 3) walking ability, 4) normal work (includes both work outside the home and housework), 5) relations with other people, 6) sleep, and 7) enjoyment of life. The arithmetic mean of the 7 interference items was used to measure pain interference.

In general, numeric rating scales for pain severity such as the BPI have been demonstrated to be valid and sensitive to change.[21] According to the American Pain Society Clinical Practice Guideline for the Management of Cancer Pain in Adults and Children,[22] NRS measures are among the most common, valid, and reliable measures used to assess cancer pain severity. The BPI is available and has been administered and assessed for validity in several languages including Spanish, French, Japanese, Chinese, Italian, Hindi, German, Greek, and Vietnamese.[23-29]

c. Assessment of predictors: clinical and demographic covariates

In addition to the pain assessments, subjects were asked to provide demographic, clinical, and outcomes information through interviews, written questionnaires, and physical examinations, to complete the clinical case report form and other original clinical trial source documents in accordance with the study protocol. Comparisons between the treatment arms are not a part of the present study. Analyses comparing treatment arms have already been conducted and are reported elsewhere.[30] The present study groups all the patients together for the analysis and assesses the predictive value of baseline and time-dependent covariates with respect to the pain outcomes.

Baseline characteristics include age, education (1 = college degree, 0 = no college degree), employment status (1 = full-time, 0 = other), geographic region (North America, South America, Europe, or Other – defined per-country in the Patients and Procedures section), antineoplastic therapy on study entry (chemotherapy plus hormonal therapy vs. hormonal therapy only), previous skeletal complications (0 = no, 1 = yes), and time from initial bone metastasis to randomization. Skeletal complications are referred to as skeletal-related events (SREs) and were defined in the trial as experiencing one or more of the following: pathologic fractures, spinal cord compression with vertebral compression fracture, the need for surgery to treat or prevent pathologic fractures or spinal cord compression, or the need for radiation to bone.[31]

The following time-dependent characteristics (i.e., status during a given interval) were included: active/restricted performance status (1 = active [ECOG status of 0 or 1], 0 = restricted [ECOG status of 2, 3, or 4]), hospital admission (including day admission, overnight admission, or other), surgery, chemotherapy treatment, and radiation treatment.

d. Statistical analysis

We conducted the analyses using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). Analyses were conducted on the intent-to-treat sample, which included all female breast cancer patients who had been randomized in the trial (n=1124). We calculated descriptive statistics for baseline and time-dependent demographic characteristics and clinical variables. We used Chi-square tests, T-tests, and Wilcoxon rank-sum tests to assess baseline differences by race for each predictor and outcome variable. We assessed extent of missing data of the outcome variables at each study visit when pain had been assessed in the trial. Some patients had missing pain outcome data at every visit. Our pain outcomes analyses exclude these patients (n = 73 completely missing for severity, leaving an analysis sample of n = 1051 for the severity scale, and n = 77 completely missing for interference, leaving an analysis sample of n = 1047 for the interference scale). We conducted exploratory analyses of the race variable using visual examination of Kaplan-Meier survival curves, with a continuous time assumption. For these analyses, failures were defined as first occurrence of reaching a 7 on the severity and interference scales.

For both the clinical and statistical interest of cutpoint 7 on the BPI, we chose to model the hazards for time to first occurrence of a 7 or above on each scale. The trial data assessment schedule involved visits scheduled every 21 days, with BPI assessments every 2 visits and ECOG assessments every 4 visits. The pain severity questions were asked over the timeframe of the past seven days (with the exception of "describe your pain right now") and the pain interference questions were asked over the timeframe of the past 24 hours. This means that gaps in information as long as 5 weeks exist in the severity data, and even longer gaps exist in the interference data. Given these gaps in information, the present study

involved interval-censored data because a patient could have experienced an event between two assessments but the exact date of the event is unknown. Interval-censored data may be analyzed under an assumption of categorical rather than continuous time at risk for hazards models. We handled this assumption using a piecewise exponential model (using PROC GENMOD) with categorized time in Poisson regression. As adapted from Stokes, Davis and Koch, *Categorical Data Analysis using the SAS System* (2000), the piecewise exponential likelihood for the present models, with continuous covariates, is as follows:

$$\Phi_{PE} = \prod_{i=1}^{n} \prod_{k=0}^{m_i} \lambda_{ik} \left\{ \exp\left[-\lambda_{ik}^{y_{ik}} N_{ik} \right] \right\}$$

where y_{ik} is equal to 1 if the event occurred, or 0 if the event did not occur for the *i*th person during the *k*th interval, N_{ik} is the total person-time of exposure (in days), m_i is the maximum number of intervals for subject *i*, and λ_{ik} is the hazard parameter. The piecewise exponential model assumes that there are conditionally independent exponential distributions with hazard parameters λ_{ik} for the respective time periods.[32] The properties of this method enable us to obtain effect estimates from Poisson regression computations using the assumption of the piecewise exponential model, regardless of whether we make the conditional arguments necessary to assume a Poisson distribution. Stokes and colleagues (2002) discuss these specific properties further.[32]

For the categorical data analysis, intervals were assigned as every 80 days following randomization, with a total of 5 intervals. Intervals were numbered 0 through 4, with the last interval beginning 320 days following randomization, and ending at 400 days (57 weeks) following randomization. Interval 0, also called the "first interval" was the referent and was 80 days in length. Although the choice of interval length and number of intervals can be

completely arbitrary for the piecewise exponential model to still be valid,[33] we chose the 80-day interval length based on the distribution of events in the intervals; model convergence requires a minimum number of events in any given interval.

For any interval in which a patient remained in the study but did not reach the outcome, time at risk was set at 80 days. A patient's last interval was the interval in which she (a) reached the outcome of a 7 or above, (b) dropped out before the 400-day mark, or (c) died before the 400-day mark. For those who reached the outcome, in their last interval an event indicator variable was set to 1, and time at risk in the last interval was defined as the time from the beginning of the interval to the date of the report of a 7 or above. For patients who dropped out early or died, time at risk in the last interval was equal to the number of days from the beginning of the last interval to the date of dropout or death. If a patient never reached the outcome in *any* interval, that observation was censored, such that the event indicator variable was set to 0 for all intervals, and time at risk within each interval was assigned as 80 (or, in the cases of dropout or death, the time at risk in the last interval would be the number of days from the beginning of their last interval to the date of dropout or death).

To account for within-subjects correlation of multiple outcome assessments over time, we used generalized estimating equation (GEE) methods to adjust the standard errors and confidence intervals around the estimated model parameters. We assessed model fit by evaluating the significance at a criterion of $\alpha = 0.05$ of the Residual χ^2 score statistic for contribution of covariates and all possible time-by-covariate interaction terms not included in the model.

These data presented an opportunity to explore the relationship between the BPI intensity composite score and the BPI interference composite score. Both are on the same numeric rating scale from 0-10, with 10 indicating greatest severity or interference. To explore the relationship of these two subscales, we explored the similarities and differences in how sets of explanatory covariates affected pain severity versus interference outcomes.

e. Sensitivity analyses

Censoring deaths versus assigning worst pain score

An overarching issue that affected all the survival analyses was that in the analyses, we may account for deaths in two ways: 1) by censoring them, 2) by treating them as events (severe pain). We conducted a sensitivity analysis to address this issue. For those patients who discontinued due to death, instead of censoring their observation, we assigned time to reach severity of 7 or higher as if the patient had reported a BPI score of 10 for the first missing pain assessment in the string of missing pain assessments following their dropout (the dropout date was effectively either the last day of enrolment in the trial, or the last day the BPI was administered, whichever was greater of the two).

Handling missing data

The survival analysis techniques required that we make certain assumptions about how to code the event indicator and time at risk variables, given missing data scenarios present in the data. There were four possible such scenarios, for which we implemented the following coding for event indicator and time-to-event variables, prior to conversion to the interval-structured data set:

- (Scenario A) if a patient reached a BPI measurement of [3,4,5,6, or 7] (hereafter referred to as “the outcome”) then the dichotomous event indicator variable was set

equal to 1 and time at risk was set equal to the number of days from randomization to the date of the first occurrence of the outcome.

- (Scenario B) If the patient had complete BPI data but never reached the outcome, then the dichotomous event indicator variable was set equal to 0 and time at risk was set equal to total number of days the patient was in the study (leading to these observations being censored in the survival analysis).
- (Scenario C) If a patient did not have any BPI data then the patient was not included in the survival analysis.
- (Scenario D) If the patient had some BPI data but never reached the outcome, then the dichotomous event indicator variable was set equal to 0. The observation was censored as in Scenario B, but total time at risk was set equal to either the total number of days the patient was in the study (assumption D.i), or to the number of days from randomization to the date of the preceding non-missing BPI measurement (assumption D.ii). We conducted a sensitivity analysis to assess the impact of different missing data handling methods, using these two variations of Scenario D (D.i and D.ii).

Another missing data handling technique used was to code the full-time employment and college education variables (each of these variables had about 16% missing data at baseline) as three-level categorical variables, with the categories as "yes", "no", or "missing", with "no" as the referent category. This technique prevents these observations from being dropped from the models.

3. Results

Table 1 presents a summary of baseline characteristics of the sample and missing data for each of the baseline covariates. The only variable for which more than 1% of patients had missing observations at baseline was the employment status variable, which was missing for 16% of the sample. However, only 14% of patients reported being employed full-time at the time of randomization. This is likely due to the fact that all patients in the trial had metastatic disease at enrollment.

The most frequent reasons for dropout were adverse events (30% of trial "completers" – those who completed a case report form at visit 19) and death (26% of noncompleters). For the entire trial population, approximately 52% of adverse events experienced were bone pain, making it the most frequent type of adverse event. The implications of this fact with regards to the proportional hazards assumption are addressed in the sensitivity analysis. Table 2 shows the study population remaining at each scheduled BPI assessment visit (visits 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, and 19) and these patients' rates of completion of the BPI severity and interference assessments. Of the 438 patients (39% of the original 1124 enrolled) who did not complete visit 19, 132 patients (30%) discontinued the study due to adverse events, and 113 patients (26%) discontinued due to death. Additional details regarding patient disposition for the overall clinical trial are reported by Rosen et al.[30] Of those patients enrolled in the trial at any given visit, the proportion who had completed BPI assessments was consistently no less than 82%.

Table 3 shows how the baseline characteristics and outcomes differed by race at the time of randomization. A majority (84%) of the total of non-Caucasian patients (n = 133) were from North American sites (n = 112). There were no baseline differences by

race in ECOG performance status, education, employment, experience of a previous SRE, or time from first bone metastasis to randomization. Caucasian patients had slightly higher mean age (57.9 ± SD12.7) compared to the mean for non-Caucasian patients (54.8 ± SD11.0). Non-Caucasian patients had higher baseline pain severity and interference scores than Caucasian patients. The median severity score was 0.63 points higher for non-Caucasians and the mean interference score was 0.86 points higher for non-Caucasians as compared with Caucasians.

Figures 1 and 2 display Kaplan-Meier survival curves that show differences by race in hazards of reaching a 7 or above for both the severity and interference scales. Evidence for statistical significance of these differences, using a criterion of $\alpha = 0.05$, is confirmed by the log-rank test statistics of 20.9 ($p < 0.0001$) and 8.6 ($p = 0.0033$), respectively.

The interval-censored nature of these data as a result of the trial visit schedule is supported by the graphic shown in Figure 3, which shows the distribution of BPI assessments around each scheduled trial visit. There appear to be more discrete intervals toward the beginning of the observation period, and more overlap in BPI assessment times later in the trial (e.g., a person whose BPI assessment took place on their 300th day post-randomization could have had that assessment labeled as having taken place at either visit 14 or visit 16).

We fit models to data structured by intervals assigned at every 80 days, and truncated at the end of Interval 4 (321-400 days post-randomization). Tables 4 and 6 show the parameters resulting from these models for the pain severity and interference outcomes, respectively. For each model, the intercept (α) represents the log incidence density for all referent categories (including non-Caucasian race) at the referent (lowest) interval.[32] The model parameter

coefficients reflect increases or decreases in incremental log incidence density. We used a significance criterion of $\alpha = 0.05$ to evaluate the contribution of each variable to the models.

The pain severity results in Table 4 show that Caucasian race and active ECOG status were associated with decreases in log incidence density, and radiation treatment since the last study visit was associated with an increase in log incidence density for pain severity of 7 or more. Also for the severity outcome, Table 5 displays, for the severity scale, the estimated failure rates (incidence densities) and concomitant cumulative "survival" rates for non-Caucasian and Caucasian patients at each interval ("survival" in quotes because it refers not to mortality but to the probability of reaching an interval without experiencing pain of 7 or above, denoting *treatment* failure. The estimated survival rate at the first interval was 0.92 for Caucasian patients versus 0.80 for non-Caucasian patients. In subsequent intervals, these rates declined similarly for Caucasian and non-Caucasian patients, but the cumulative survival rate for Caucasians in the last interval (0.84) was still higher than the rate for non-Caucasians in the first interval.

Table 6 shows that for the pain interference outcome, Caucasian race, age in decades, and active ECOG performance status were associated with decreases in log incidence density. However, the GEE-adjusted confidence limits for the effect of age upon hazards for pain interference did not exclude the null value. Hospital admission since the last study visit, and radiation treatment since the last study visit were each associated with increases in log incidence density for pain interference of 7 or more. Table 7 contains the estimated failure rates (incidence densities) and concomitant cumulative survival rates for non-Caucasian and Caucasian women at each interval for the interference outcome. The estimated survival rate at the first interval was 0.80 for Caucasian women versus 0.70 for non-Caucasian women. As

with the severity outcome, in subsequent intervals, these rates declined similarly for Caucasian and non-Caucasian women, but the cumulative survival rate for Caucasians in the last interval (0.71) was still better than the rate for non-Caucasians in the first interval.

All results were robust in direction, magnitude, and statistical significance with regard to the two sensitivity analyses varying assumptions in (a) counting of deaths and (b) handling of missing data.

Table 12. (MS2: Table 1). Baseline patient characteristics and missing data (N = 1124).

Characteristic	Values[A]	Number of patients with values missing at baseline (%)
Age in years, mean ± SD	57.5 ± 12.6	0 (0)
Female	1124 (100)	0 (0)
Caucasian race	991 (88)	0 (0)
College education	281 (25)	186 (17)
Employed full-time	157 (14)	182 (16)
Geographic region [B]		0 (0)
North America	773 (69)	
Europe	217 (19)	
South America	39 (3)	
Other	95 (8)	
Baseline ECOG performance status		4 (0.4)
Active (0 or 1), recoded as 1	952 (85)	
Restricted (≥2), recoded as 0	168 (15)	
Antineoplastic therapy (trial stratification variable)		0 (0)
Chemotherapy	525 (47)	
Hormonal therapy	599 (53)	
Experienced previous skeletal related	677 (60)	3 (0.3)

Characteristic	Values[A]	Number of patients with values missing at baseline (%)
event		
Time from first bone metastasis to randomization, days	157 (14)	3 (0.3)
Mean ± SD	406 ± 744	
Median	108	

[A] Values are expressed as number (percentage) unless otherwise indicated.
[B] Variable is dichotomized to North America / Other for present analyses.
Some totals do not add up to 100% due to rounding.
SD = Standard deviation
ECOG = Eastern Cooperative Oncology Group

Table 13. (MS2: Table 2). Study population and Brief Pain Inventory (BPI) completion at each scheduled assessment

Visit	Study Population [A]	Completeness of BPI Composite Scores			
		Severity Score		Interference Score	
		n (% of pts. in trial at visit *i*) [B]	(% of starting N)	n (% of pts. in trial at visit *i*) [B]	(% of starting N)
Visit 2	1124 (100)	1024 (91)	(91)	1029 (92)	(92)
Visit 3	1117 (99)	975 (87)	(87)	972 (87)	(86)
Visit 4	1073 (95)	950 (89)	(85)	953 (89)	(85)
Visit 6	1019 (91)	898 (88)	(80)	906 (89)	(81)
Visit 8	942 (84)	806 (86)	(72)	807 (86)	(72)
Visit 10	896 (80)	794 (89)	(71)	798 (89)	(71)
Visit 12	812 (72)	675 (83)	(60)	675 (83)	(60)
Visit 14	784 (70)	673 (86)	(60)	681 (87)	(61)
Visit 16	706 (63)	598 (85)	(53)	599 (85)	(53)
Visit 18	672 (60)	551 (82)	(49)	549 (82)	(49)
Visit 19	686 (61)	584 (85)	(52)	583 (85)	(52)

[A]Indicates the number (percent) of patients remaining in the study at each scheduled BPI assessment visit.

[B]Indicates number of patients at each BPI assessment for whom BPI Composite Scores could be calculated.

Table 14 (MS2: Table 3). Baseline characteristics by race[A]

	Race		Test statistic: baseline differences	P-value
	Caucasian	Non-Caucasian		
Categorical baseline variables				
Geographic Region				
European Union	212 (21)	5 (4)		
North America	661 (67)	112 (84)	6.08 [B]	0.014
South America	38 (4)	1 (1)		
Other	80 (8)	15 (11)		
Baseline ECOG performance status				
Active (0 or 1)	85 (37)	111 (84)	0.10 [B]	0.756
Restricted (2)	147 (63)	21 (16)		
College education				
Yes	247 (27)	34 (28)	0.14 [B]	0.705
No	580 (62)	76 (62)		
Missing	102 (11)	12 (11)		
Employed full-time				
Yes	138 (15)	19 (16)	0.06 [B]	0.811
No	693 (75)	91 (75)		

	Race		Test statistic: baseline differences	P-value
	Caucasian	Non-Caucasian		
Missing	98 (11)	12 (10)		
Previous skeletal related event				
Yes	599 (61)	78 (59)	0.19 [B]	0.661
No	389 (39)	55 (41)		
Continuous variables				
Age in years, mean ± SD	57.9 ±12.7	54.8 ±11.0	-3.05 [C]	0.003
Time from first bone metastasis to randomization in days, median (IQ range)	103 (36 - 473)	124 (36 - 606)	0.20 [C]	0.654
Continuous outcomes				
BPI Composite Score - Severity, median (25%-75% interquartile range)	2.75 (1.25 - 4.50)	3.38 (1.75 - 5.75)	3.59 [C]	0.0003
BPI Composite Score - Interference, median (25%-75% interquartile range)	3.00 (0.57 – 5.42)	3.86 (1.43 - 6.86)	3.08 [C]	0.0020

[A] Values are expressed as number (percentage) unless otherwise indicated.
[B] Mantel-Haenszel Chi-Square test
[C] T-statistic for normal distribution, Wilcoxon rank sum statistic for non-normal distribution.
ECOG = Eastern Cooperative Oncology Group.

Table 15 (MS2: Table 4). Model parameters: baseline and time-dependent predictors for hazard of first reaching BPI severity score of 7 or above (categorical time assumption).

Parameter	Est.	SE	HR (e^{β_k})	Wald 95% CLs for HR	Z	p > |Z|
Intercept	-6.075	0.549	0.00	0.00-0.01	-11.06	<.0001
Caucasian	-0.889	0.209	0.41	0.27-0.62	-4.26	<.0001
College education (=1)	-0.332	0.202	0.72	0.48-1.07	-1.65	0.10
Education variable missing (=2)	0.857	0.887	2.36	0.41-13.39	0.97	0.33
< College education (=0, ref.)	.	.	.	.	.	.
Employed full-time (=1)	-0.277	0.280	0.76	0.44-1.31	-0.99	0.32
Employment status missing (=2)	-0.675	0.918	0.51	0.08-3.08	-0.74	0.46
Not employed full-time (=0, ref.)	.	.	.	.	.	.
Previous skeletal related event	0.170	0.176	1.18	0.84-1.67	0.97	0.33
Age in decades	0.086	0.066	1.09	0.96-1.24	1.31	0.19
Admitted to hospital[A]	0.103	0.231	1.11	0.71-1.74	0.45	0.65
Active ECOG status[A]	-0.611	0.197	0.54	0.37-0.80	-3.11	0.002
Surgery[A]	0.172	0.376	1.19	0.57-2.48	0.46	0.65
Radiation therapy[A]	1.155	0.220	3.17	2.06-4.89	5.24	<.0001
Chemotherapy[A]	0.249	0.173	1.28	0.91-1.80	1.44	0.15
Interval 1: 81-160 days	-1.828	0.280	0.16	0.09-0.28	-6.53	<.0001
Interval 2: 161-240 days	-1.349	0.247	0.26	0.16-0.42	-5.46	<.0001

Parameter	Est.	SE	HR (e^{β_k})	Wald 95% CLs for HR	Z	p > |Z|
Interval 3: 241-320 days	-1.339	0.272	0.26	0.15-0.45	-4.92	<.0001
Interval 4: 321-400 days	-1.439	0.343	0.24	0.12-0.46	-4.19	<.0001
Interval 0 (referent): 0-80 days	.	.	.	.	.	.

[A]Time-dependent covariates – recorded as since the last study visit.

Note: SE = standard error. HR = hazard ratio. CLs = confidence limits. ECOG status = Eastern Cooperative Oncology Group performance status. Ref. = referent category. SEs and related values are adjusted using generalized estimating equation (GEE) methods.

Table 16. (MS2: Table 5). Model-based 400-day outcome probabilities by race: failure is first occurrence of pain score 7 or higher on the BPI severity scale.

Characteristic	Interval	Incidence Density (Estimated Failure Rate)	Estimated Cumulative Survival[A] Rate
Non-Caucasian	0 (0-80 days)	0.0028	0.7993
Non-Caucasian	1 (81-160 days)	0.0004	0.7741
Non-Caucasian	2 (161-240 days)	0.0007	0.7319
Non-Caucasian	3 (241-320 days)	0.0007	0.6920
Non-Caucasian	4 (321-400 days)	0.0007	0.6543
Caucasian	0 (0-80 days)	0.0011	0.9158
Caucasian	1 (81-160 days)	0.0002	0.9013
Caucasian	2 (161-240 days)	0.0003	0.8799
Caucasian	3 (241-320 days)	0.0003	0.8590
Caucasian	4 (321-400 days)	0.0003	0.8386

Note: referent is based on coefficients multiplied by population proportions (for categorical variables) or population mean (for age).

[A]Survival does not indicate mortality, but rather reaching a given interval without having reached a pain score of 7.

Table 17. (MS2: Table 6). Model parameters: baseline and time-dependent predictors for hazard of first reaching BPI interference score of 7 or above (categorical time assumption).

Parameter	Est.	SE	HR (e^{β_k})	Wald 95% CLs for HR	Z	p > |Z|
Intercept	-3.772	0.436	0.02	0.01-0.05	-8.65	<.0001
Caucasian	-0.514	0.190	0.60	0.41-0.87	-2.71	0.007
College education (=1)	-0.193	0.158	0.82	0.61-1.12	-1.23	0.220
Education variable missing (=2)	0.308	0.536	1.36	0.48-3.89	0.58	0.565
< College education (=0, ref.)	.	.	.	.	.	.
Employed full-time (=1)	-0.333	0.209	0.72	0.48-1.08	-1.60	0.111
Employment status missing (=2)	-0.257	0.565	0.77	0.26-2.34	-0.45	0.650
Not employed full-time (=0, ref.)	.	.	.	.	.	.
Previous skeletal related event	0.239	0.137	1.27	0.97-1.66	1.74	0.082
Age in decades	-0.162	0.054	0.85	0.76-0.95	-2.98	0.003
Admitted to hospital[A]	0.622	0.166	1.86	1.34-2.58	3.74	0.000
Active ECOG status[A]	-1.112	0.148	0.33	0.25-0.44	-7.49	<.0001
Surgery[A]	-0.251	0.296	0.78	0.44-1.39	-0.85	0.395
Radiation therapy[A A]	0.983	0.187	2.67	1.85-3.86	5.25	<.0001
Chemotherapy[A]	0.025	0.141	1.02	0.78-1.35	0.17	0.862
Interval 1: 81-160 days	-2.067	0.216	0.13	0.08-0.19	-9.56	<.0001
Interval 2: 161-240 days	-2.182	0.250	0.11	0.07-0.18	-8.74	<.0001

Parameter	Est.	SE	HR (e^{β_k})	Wald 95% CLs for HR	Z	p > |Z|
Interval 3: 241-320 days	-1.682	0.217	0.19	0.12-0.28	-7.74	<.0001
Interval 4: 321-400 days	-1.747	0.273	0.17	0.10-0.30	-6.41	<.0001
Interval 0 (referent): 0-80 days	.	.	.	.	.	.

[A]Time-dependent covariates – recorded as since the last study visit.

Note: SE = standard error. HR = hazard ratio. CLs = confidence limits. ECOG status = Eastern Cooperative Oncology Group performance status. SEs and related values are adjusted using generalized estimating equation (GEE) methods.

Table 18. (MS2: Table 7). Model-based 400-day outcome probabilities by race: failure is first occurrence of pain score 7 or higher on the BPI interference scale.

Characteristic	Interval	Incidence Density (Estimated Failure Rate)	Estimated Cumulative Survival[A] Rate
Non-Caucasian	0 (0-80 days)	0.0046	0.6921
Non-Caucasian	1 (81-160 days)	0.0006	0.6597
Non-Caucasian	2 (161-240 days)	0.0005	0.6338
Non-Caucasian	3 (241-320 days)	0.0009	0.5898
Non-Caucasian	4 (321-400 days)	0.0008	0.5532
Caucasian	0 (0-80 days)	0.0028	0.7993
Caucasian	1 (81-160 days)	0.0003	0.7803
Caucasian	2 (161-240 days)	0.0003	0.7618
Caucasian	3 (241-320 days)	0.0005	0.7319
Caucasian	4 (321-400 days)	0.0003	0.7145

Note: referent is based on coefficients multiplied by population proportions (for categorical variables) or population mean (for age).

[A]Survival does not indicate mortality, but rather reaching a given interval without having reached a pain score of 7.

Figure 21. (MS2: Figure 1). Survival distribution function (continuous time assumption) for first occurrence of 7 on pain severity scale, by race.

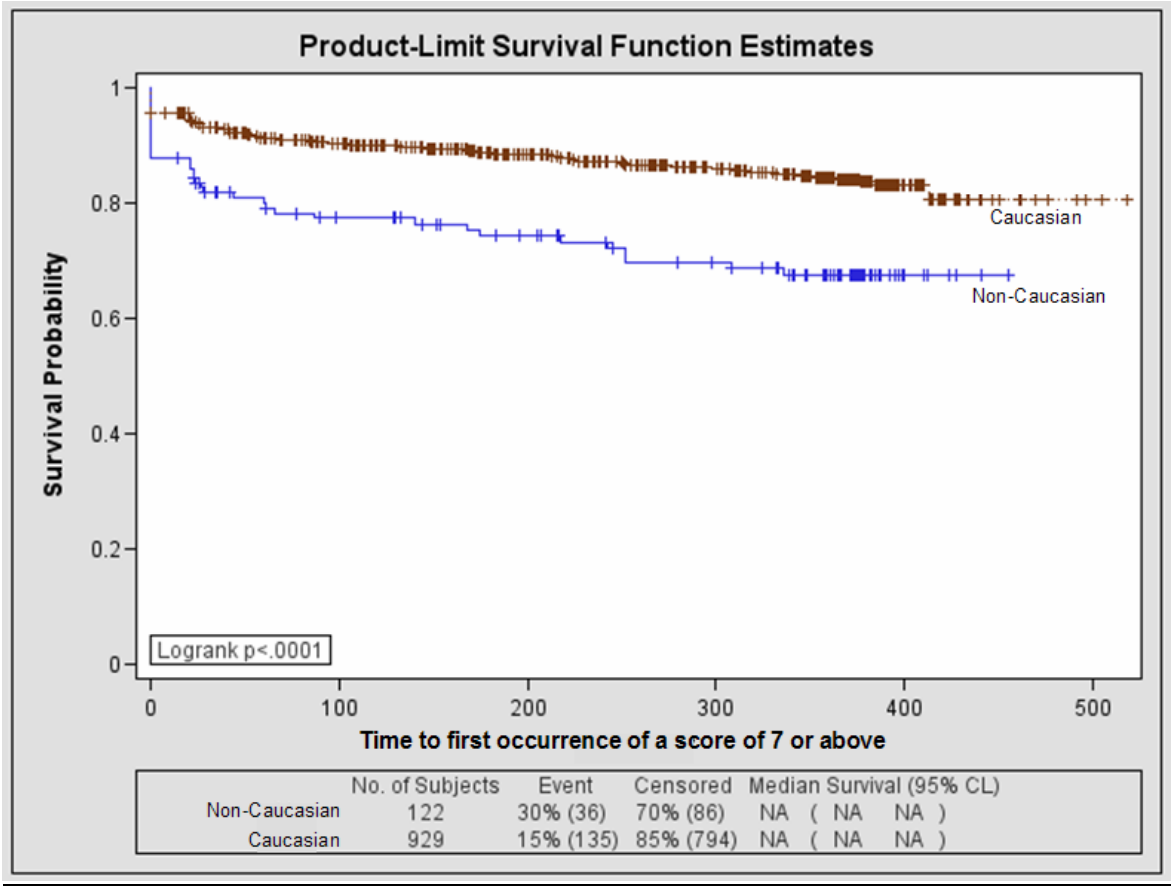


Figure 22. (MS2: Figure 2). Survival distribution function for first occurrence of 7 or above on pain interference scale, by race.

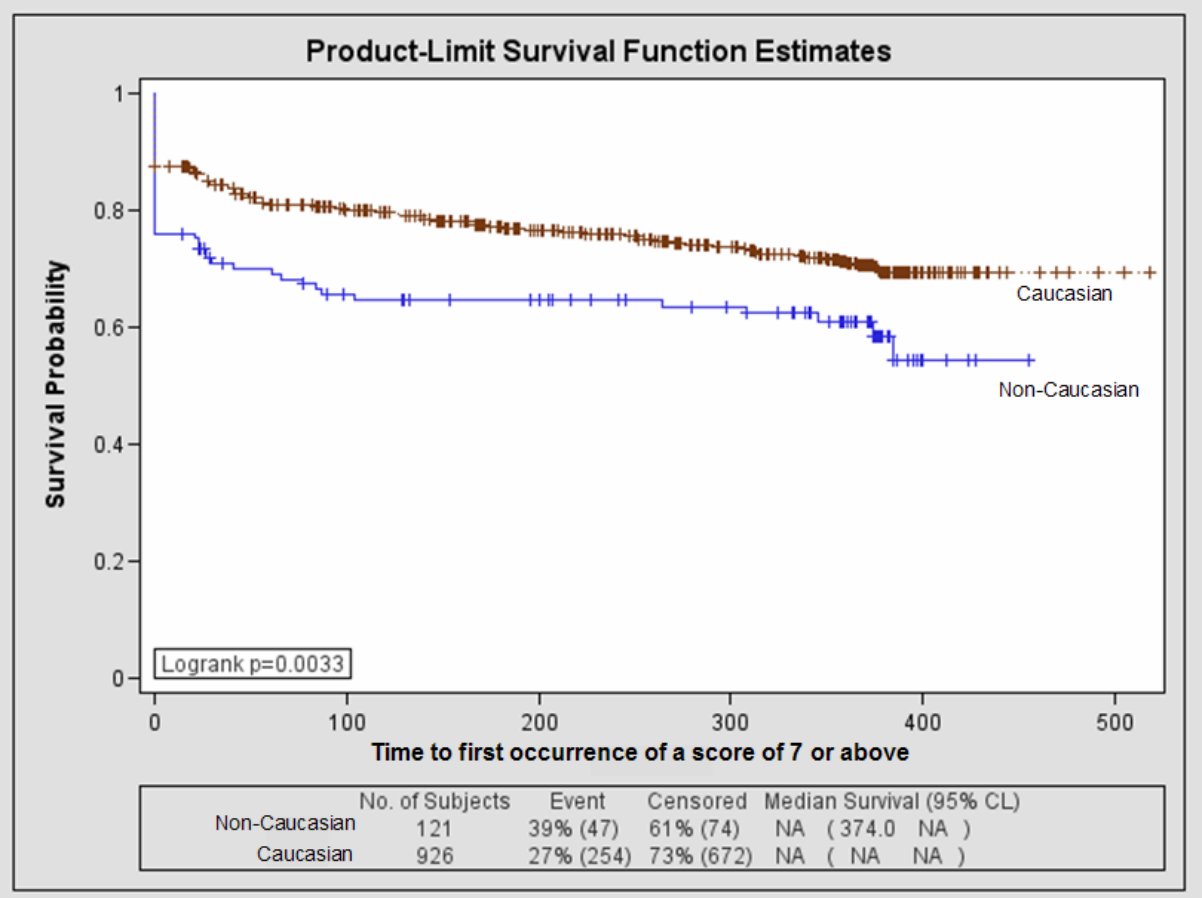
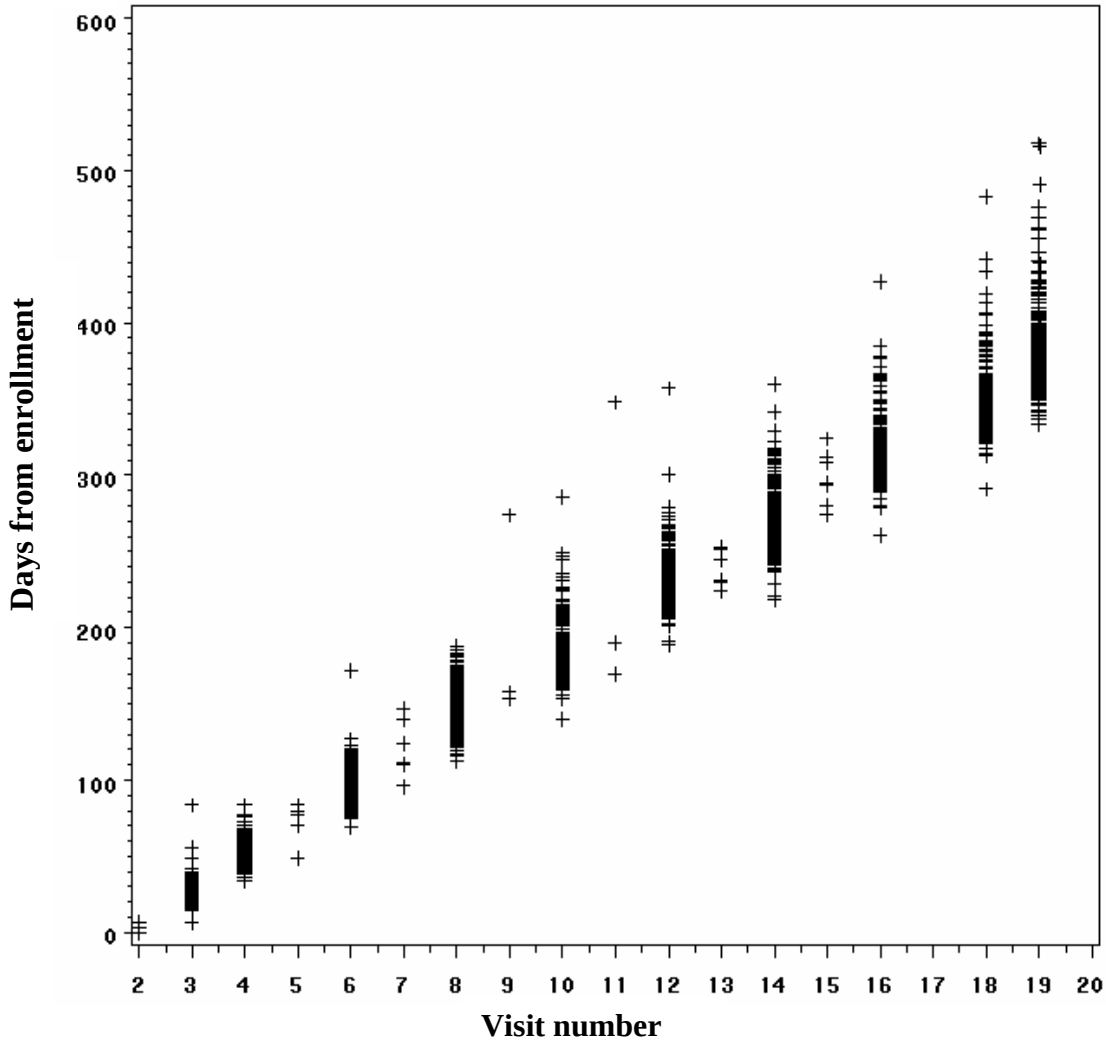


Figure 23. (MS2: Figure 3). Distribution of visit windows around scheduled BPI visit dates



BPI = Brief Pain Inventory

4. Discussion

The 2001 AHRQ evidence review entitled Management of Cancer Pain states that "investigations of cancer pain and its control should seek to evaluate the influence of gender, race, age, psychosocial context, ethnicity, and culture on the experience and report of pain."[10] The present study aimed to assess differences in time to first reaching a pain severity or interference score of 7 or above on the 0-10 BPI scales among women with metastatic breast cancer, using hazards models that account for interval-censored data collected at multiple assessments per patient as part of a clinical trial. Our secondary analyses of these longitudinal data estimated the associations of a set of baseline and time-dependent clinical and demographic characteristics with hazards for these two pain outcomes, compared the two scales for similarity in the sets of predictors found to be associated with higher or lower hazards over the course of 400 days post-randomization, and investigated the hypothesis that, as compared with their Caucasian counterparts, non-Caucasian women would have higher hazards of pain severity and pain interference in daily functions. In the present study, survival rates refer not to mortality rates, but instead to rates, derived from hazard rates, of patients' survivorship over time in not reaching a 7 on a given outcome scale. When a patient reaches a 7, this event may be considered a "treatment failure" because successful pain management should have prevented the patient from reaching pain at or near the levels of highest intensity that she can imagine. It is important to note that although the 7 cutoff is used for these analyses, there is debate over the classification of severe pain; in practice even a score of 5 may be considered severe, and thus a indication for palliative intervention.

For the pain severity outcome, Caucasian race and active ECOG performance status were associated with decreases in log incidence density, and radiation treatment since the last

study visit was associated with a concomitant increase in log incidence density for the severity outcome. For the pain interference outcome, Caucasian race, higher age in decades, and active ECOG performance status were associated with decreases in log incidence density for the outcome. Hospital admission since the last study visit, and radiation treatment since the last study visit were each associated with greater pain interference in a given interval.

For both pain severity and interference, non-Caucasian women started the study with worse scores; the probability of making it through any given interval without experiencing a 7 or more on either scale was lower for non-Caucasian women. Although the rates of change in incidence density over time are comparable by race, the Interval 1 survival rate for non-Caucasian race was still lower than the Interval 4 survival rate for Caucasian race. These findings support the hypothesis that non-Caucasian race is associated with worse pain severity and interference outcomes, not only cross-sectionally, but also longitudinally among women with metastatic breast cancer.

Neither surgery nor chemotherapy was found to be associated with higher pain hazards in a given interval, but radiation therapy had the highest association with greater pain intensity, as compared with all of the other covariates assessed. These findings are consistent with the concepts that (a) therapeutic benefits from chemotherapy and surgery may outweigh temporary pain associated with these interventions, and (b) a patient's report of severe pain would cue the treating physician to initiate a round of radiation therapy. Within a given interval, it is more likely that pain precedes and even causes radiation therapy.

Hospital admission since the last visit was found to be associated with reaching a 7 for the pain interference outcome, but not for the pain severity outcome. Hospital admission may have a greater impact on patients' perceived levels of pain interference in their daily

activities than on patients' perceived levels of pain severity. We may attribute this finding to the fact that once admitted to a hospital, patients may get more analgesic treatment and pain management than they would outside the hospital, but their daily activities would be disrupted by the admission. A limitation of the data used for the present analyses is ambiguity about temporality of events within intervals. This limitation precludes causal inferences with regard to the time-dependent variables.

Another weakness of the present study is that although the dataset used contains pain information at multiple assessment times per patient, some gaps in the data exist. Gaps of at least one week in information exist in the BPI scores, and all pain events of interest are not captured; a patient could have experienced an event between two assessments but the exact date of the event is unknown. Ideally, pain would be assessed at shorter intervals to gather more complete information - multiple assessments per day, for every day of observation would be ideal. If a pain assessment instrument asks about the last 7 days, to gain complete information over time, the measure should be administered every 7 days. The impact of this limitation on the present study is that although we are able to assess pain hazards over time based on the information available, pain may have increased or decreased during the gaps between assessments. The piecewise exponential model helps accommodate these gaps, but more complete pain information without gaps would be desirable.

This analysis was limited also by the characteristics of the clinical trial, which was designed to answer research questions about the relative efficacy of the two bisphosphonates. Limitations were imposed by the exclusion criteria and the covariates that were collected in the clinical trial. Future research should collect and model simultaneously the longitudinal

effects of these and other psychological, sociocultural, health care-level, and clinical characteristics known to affect pain.

One strength of the present study is that it improves upon previous simple change-from-baseline analyses, offering more information about pain intensity outcomes over the course of treatment. Change-from-baseline methods ignore considerable amounts of data collected during the trial, and are at best sub-adequate when used to compare health-related quality of life (HRQoL) outcomes among treatment groups in clinical trials. The present study utilizes BPI data collected at multiple assessment times over 400 days.

Another strength is the robustness of the piecewise exponential model with 80-day intervals in modeling pain severity and interference outcomes. The two main difficulties in the analysis of data from repeated measures studies are 1) complication of the analysis by the dependence among repeated observations made on the same experimental unit (the patient in this case), and 2) imbalanced or partially incomplete data.[32] The present study addresses these two challenges by 1) using GEE methods to account for the interdependence of multiple observations for each patient, and testing assumptions about handling of missing data due to death or early discontinuation.

Future analyses of these data should comprise multivariate analyses that accommodate interval-censored data and include both baseline and other time-dependent covariates. Such analyses would provide more comprehensive information about predictors for the multiple outcomes on both the pain severity and interference subscales of the BPI. In addition, future analyses should account for multiple failures over time (e.g., a patient reaching severe pain, then experiencing a decrease in pain, then reaching severe pain again during the course of treatment).

Data collection in clinical trials can be improved for the purpose of epidemiologic study; given the marginal efforts and expenses in relation to the trial itself, it is of great informational benefit to incorporate into trial designs prospective, comprehensive assessments of pain in longitudinal tumor-specific cohorts, and to specifically target sources of racial disparities in this endeavor.

Our findings that race was an important predictor of pain over time are consistent with other risk factor studies and clinical practice guidelines,[34] including reports and extensive reviews that conclude that minority patients have been found consistently to be at greater risk of having undertreated pain and worse pain outcomes.[4,5,35,36] Our findings with regard to restriction/impairment as measured over time by ECOG performance status offer longitudinal evidence to confirm that performance status is an important predictor of pain and other health-related quality of life outcomes.[37,38] In confirming these characteristics as risk factors over time among women with metastatic breast cancer, our findings should help to inform individual prognoses and pain management strategies according to patient attributes that are available for assessment over time. Early intervention and more aggressive pain management strategies should be implemented to prevent worse outcomes among those at highest risk over the course of treatment for severe pain and high levels of pain interference in daily activities.

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CHAPTER VI

CONCLUSIONS

A. Recapitulation of overall study aims, findings and degree to which the goals of the doctoral research have been met

1. Overall study aims

The over-reaching goal of this project was to better understand risks and risk factors for pain severity and interference outcomes over the course of disease among patients with metastatic breast cancer. Manuscript 1 addresses Aims 1 and 2 below, and Manuscript 2 addresses Aims 2, 3, and 4. We hope that this research underscores the need for improvement in pain management strategies, and provides tools to effect improvements in these strategies through better prediction of pain outcomes over time.

AIM 1: To provide descriptive epidemiologic information about pain hazards over time among patients with metastatic breast cancer, exploring the effect of using different intensity cutpoints on the Brief Pain Inventory (BPI) severity and interference 0-10 subscales with regard to baseline clinical and demographic covariates as risk factors.

Research question: What are the hazards of reaching different pain severity and interference thresholds over 51 weeks, and what baseline clinical and demographic factors are associated with occurrence of these outcomes?

AIM 2: To explore the relationship between the pain severity and interference BPI subscales with regard to sets of clinical and demographic covariates as predictors.

Research question: Given that the relationship between the severity and interference

subscales of the BPI is nonlinear, how do clinical and demographic predictors compare in their associations with hazards over time for pain severity and interference outcomes?

AIM 3: To estimate the effects of both baseline and time-dependent clinical and demographic characteristics on time to first reaching a pain severity or interference score of 7 or above on the 0-10 BPI severity and interference scales.

Research question: How do baseline and time-dependent risk factors predict the outcomes of reaching a 7 or above on the BPI severity and interference scales?

AIM 4: To investigate the hypothesis that, as compared with their Caucasian counterparts, non-Caucasian patients would have worse longitudinal outcomes with regard to (a) pain severity, and (b) pain interference in daily functions.

Research question: Within our sample of longitudinal data collected in a clinical trial among patients with metastatic breast cancer, will our findings confirm existing findings of racial/ethnic disparities in the burden of pain? Also, with regard to hazards for these pain outcomes, how does the race variable fit in with other baseline and time-dependent clinical and demographic factors in a predictive model?

2. Findings

Our findings from the analyses conducted for Manuscript 1 that non-Caucasian race, younger age, and impaired performance status are important predictors of pain over time are consistent with previous cross-sectional risk factor studies and with clinical practice guidelines. In confirming these characteristics as predictors of pain hazards over time in metastatic breast cancer, our findings inform individualized prognoses for pain outcomes according to baseline patient attributes. Early intervention and more aggressive pain management strategies can be tailored to these personalized prognoses over the course of

treatment to delay first occurrence of higher pain scores among those at greater risk for severe pain and pain interference in daily activities. The findings from the multivariate pain severity analysis indicate that non-Caucasian women are at greater hazard of reaching higher pain severity scores earlier than their Caucasian counterparts. The interaction term for this hazard is significant at values of 5 and higher on the BPI. Given the potential risks of undertreated pain, our findings should aid in future research to evaluate the role of cutpoints in making pain treatment decisions, aimed to delay or prevent worse outcomes among those patients at greatest risk over time.

Our findings from the analyses conducted for Manuscript 2 support the hypothesis that non-Caucasian race is a risk factor for worse pain severity and interference, not only cross-sectionally, but also longitudinally among women with metastatic breast cancer. Our findings with regard to restriction/impairment as measured over time by ECOG status offer longitudinal evidence to confirm that performance status is an important predictor of pain and other health-related quality of life (HRQoL) outcomes, as well as mortality/survival. In confirming the prognostic value for pain outcomes of ECOG status and race, our findings should help to inform individual prognoses and pain management strategies according to patient attributes that are available for assessment over time. Future research should aim to assess pain comprehensively over time in tumor-specific cohorts, and to incorporate data collection designs that specifically target sources of racial disparities.

I hope that this research will underscore the need for improvement in pain management strategies, and will provide tools to effect improvements in these strategies through better prediction of pain risks over time.

3. Meeting the goals of the doctoral research

To fulfill the goals of the doctoral research, the dissertation must be of appropriate scope and substantial rigor, as judged by the committee. I have taken the role of lead investigator on the design, analysis, consultation, and writing for two manuscripts that are suitable for submission. My work has benefited from verbal and written input by the Chair and committee members, as well as through regular consultation with the UNC Biometric Consulting Laboratory. At the dissertation interim committee meeting, all members present reached consensus that the scope of the research was appropriate.

The proposal defense, preparation, submission for publication, and defense of this dissertation addresses the following specific goals enumerated in the Epidemiology Academic Policies Manual:

> "The defense of the dissertation proposal documents the ability to justify research concepts and methodology related to healthcare epidemiology and ensures that the dissertation falls within the framework of healthcare epidemiology."

The proposal defense involved presentation and justification of the concepts of importance in studying longitudinal pain outcomes in tumor-specific populations. Through ongoing consultation with the committee, I refined the scope of the dissertation such that I have used the data to explore concepts of pain measurement that are of importance and interest in the field currently. The committee found that the proposed work fell within the framework of healthcare epidemiology, and helped me refine the scope to be appropriate for the doctoral research.

> "The successful completion of defense of the dissertation further demonstrates research skills and the ability to integrate core concepts of healthcare epidemiology into research endeavors."

The defense of the dissertation should be deemed by the committee to demonstrate my research skills and ability to integrate into my research endeavors core analytic, organizational, methodological, and theoretical concepts that I have learned in the Epidemiology program.

> "Publications, in peer-reviews journals, arising from the dissertation provide further evidence, of an outcome nature, of achieving the learning objectives."

As previously stated, I have taken the role of lead investigator on the design, analysis, consultation, and writing for two manuscripts that are suitable for submission.

B. Strengths

One strength of the clinical trial design was that pain was measured at multiple time points. Because bone pain was the most frequent type of adverse event experienced by patients in this trial, it is realistic to assume that pain would be related to early termination through dropout or death. If this were the case, the censoring distribution would not be independent of the outcome, and the proportional hazards assumption would not be met. However, when we conducted sensitivity analyses varying handling of deaths and missing data, our findings did not change markedly in direction, magnitude, or statistical significance.

The large trial population of 1,124 patients may be considered a strength of the present study, assuming minimal impact of potential bias related to the sampling method on this sample's representativeness of women with metastatic breast cancer. In their 2004 study of cancer clinical trial participation, Murthy and colleagues found that younger and minority patients were less likely than their counterparts to participate in cancer clinical trials.[113] However, the distribution of race in this study (recorded as "Black" for 5.7% of the sample) appears close to the distribution of race among prevalent first malignant breast cancer cases in 2002 in the U.S. (Black = 7.4% of total cases) estimated by Surveillance, Epidemiology

and End Results (SEER).[114] With regards to age, women aged 57 years or less composed approximately half the trial population, while 20% of prevalent breast cancer cases were aged 54 or lower in 2002 U.S. estimates (27-year limited-duration prevalence, first malignant cancer only).[114] Thus, both the age and race distributions in the present study seem to represent the populations to which we would generalize the findings, although the influence of potential bias with regard to traits affecting pain outcomes cannot be ruled out entirely. According to the eligibility criteria that originally defined the patient population for the trial, the findings from the present study should be generalizeable to adult female patients with metastatic breast cancer who did not have severe cardiovascular disease, and were not pregnant.

Another strength of the present study is that because the trial was conducted in accordance with applicable regulations, quality control procedures were conducted on the data to be used. For clinical and demographic data, the pharmaceutical sponsor used a Contract Research Organization (CRO) to conduct data quality checks and queries as follows: Data items from the data collection forms (case report forms, or CRFs) were entered into the study database (Clintrial version 3) at the CRO, using double data entry with verification upon second entry. Text items (e.g. typed comments) were entered once and checked manually against the CRFs. Subsequently, the information entered into the database was systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious data entry errors were corrected by CRO personnel. Other errors or omissions were entered on Data Query Forms, which were returned to the investigational site for resolution based on source documentation. A copy of the signed Data Query Form was kept with the CRFs, and once the original was received at

the CRO, the resolutions were entered into the database. QC audits of all key safety and efficacy data in the database were made when the last query from an individual patient was returned.

Another strength of the present study is that all of the findings were robust in direction, magnitude, and statistical significance with regard to the sensitivity analyses varying assumptions about counting of deaths and missing data.

In quantifying pain over the course of treatment for metastatic breast cancer, the present study is original in filling the need for epidemiologic study of tumor-specific longitudinal pain outcomes. It is hoped that our findings will further understanding of the definition and extent of pain and its measurement. By focusing on the experience of pain over time from the patient's perspective, investigating cutpoints, and using analytic techniques that use all the data collected over the course of time among a sample of 1,124 patients, the present research should be useful to clinicians in understanding the consequences of inadequate pain management. This study should also provide valuable information to those who are designing oncology clinical trials, as well as those designing measures of PROs and patient-physician communication.

C. Limitations

One important source of error that applies to the BPI in this study (and affects the measurement of both severity and interference outcomes) is missing data. Dropout due to death or due to declines in HRQoL is expected to lead to non-random missing data patterns. The impact of using missing data imputation methods, as well as assumptions that must be made when using different models given non-random missing patterns are

investigated and addressed through the analysis procedures, in collaboration with both the statistician and the methodologist.

Another methodological limitation is that although the dataset used contains pain information at multiple assessment times per patient, some gaps in the data exist. The trial data assessment schedule involved visits scheduled every 21 days, with BPI assessments every 2 weeks and ECOG assessments every 4 weeks. All pain questions were asked over the timeframe of the past seven days (with the exception of "describe your pain right now". This means that gaps of at least one week in information exist in the BPI scores, and that a given patient could have reached a 7 on the severity or interference scale between recorded assessments. Thus, the present study involves interval censored data because a patient could have experienced an event between two assessments but the exact date of the event is unknown. Ideally, pain would be assessed at shorter intervals to gather more complete information - multiple assessments per day, for every day of observation would be ideal. If a pain assessment instrument asks about the last 7 days, to gain complete information over time, the measure should be administered every 7 days. The impact of this limitation on the present study is that although we are able to assess pain hazards over time based on the information available, pain may have increased or decreased during the gaps between assessments. The piecewise exponential model helps accommodate these gaps, but more complete information would be desirable.

This analysis was limited by the characteristics of the clinical trial, which was designed to answer research questions about the relative efficacy of two bisphosphonates. Limitations were imposed by the exclusion criteria and the covariates that were collected in the clinical trial. Future research should collect and model the effects of factors that are not in these

datasets but that are known to affect pain, such as adherence, patient and physician barriers to effective analgesic treatment (the patient portion of which can be measured through the Patient Barriers Survey[116]), and other predictors of cancer pain outcomes.

A source of error is possible data transcription, management, and transmission problems omnipresent whenever paper-based case report forms are used in clinical trials. This limitation is addressed through the QC procedures described.

Another source of error is patients underreporting or overreporting the pain they experience. Although underestimation of pain is more a problem in retrospective studies involving spontaneous patient reports,[30] it is still possible that in the present study, patients may underreport pain (there is more evidence for underreporting, rather than overreporting, being a likely problem). Based on cultural views, some patients may believe that pain is a spiritual or religious test of their faith, or believe that it is wrong to take or become addicted to opioids. These patients may therefore refuse to report their pain or accept palliative treatment.[31] When interpreting the results of the present study, we acknowledge that, due to potential and probable underreporting,[30,31,115,116] our estimates may be biased downward toward lower amounts of pain than patients actually experience. However, pain is a subjective construct, and clinicians and researchers must rely on patient report of pain; no neurophysiological or laboratory test can measure pain.[117] Addressing the limitation of underreporting at the source (i.e., at the time of the data collection) may require behavioral intervention strategies with the goal of encouraging patients to more accurately report their pain. Such interventions are beyond the scope of the present study, but are of life-and-death importance because pain is a prime indicator of disease severity that drives cancer treatment decisions. Patient

education to improve accuracy of self-reported pain may involve an ethical dilemma of asking people to possibly act in discordance with their religious or cultural beliefs, but in the name of improving disease outcomes and survival.

D. Future directions

Future analyses of these data could comprise multivariate analyses that accommodate interval-censored data and include both baseline and other time-dependent covariates. Such analyses would provide more comprehensive information about predictors for the multiple outcomes on both the pain severity and interference subscales of the BPI. In addition, future analyses should account for multiple failures over time (e.g., a patient reaching severe pain, then experiencing a decrease in pain, then reaching severe pain again during the course of treatment).

Given our findings with regards to disparities in potential risks of non-Caucasians reaching pain cutpoints 5 through 7 earlier than Caucasians, we recommend questioning the modular approach to pain management with NRS severity categories 1-4, 5-6, 7-10. The findings from the present study should aid in future research to evaluate, based on outcomes, the role of cutpoints in treatment algorithms.

The present study involves the study of patients with breast cancer. However, Novartis granted permission for me to carry out longitudinal analyses of pain in both the breast cancer sample described in the present study as well as in a sample of prostate cancer patients in a similarly constructed clinical trial (Novartis protocol number 42446-03-039: "A randomized, double-blind, placebo-controlled, multicenter, comparative, safety and efficacy study of intravenous zoledronate [4 and 8 mg] in prostate cancer patients with metastatic bone lesions receiving antineoplastic therapy", concluded in 2001). Applying the analytic approaches used

in the present study to the sample of prostate cancer patients would provide tumor-specific information on patients' experiences of pain associated with another type of cancer. This information could help clinicians, bioethicists, psychologists, sociologists, and others to better measure, understand, and manage pain among prostate cancer patients.

APPENDICES

A. IRB certification (in lieu of a copy of informed consent document)

B. Brief Pain Inventory Instrument (Excerpts: severity and interference)

C. Permission: Data Usage – Novartis Pharmaceuticals Corporation

D. Permission: BPI Data Analysis – M.D. Anderson Cancer Center

E. Permission: Cancer Incidence (Figure 2) – American Cancer Society

F. Permission: WHO Pain Ladder (Figure 4) – World Health Organization

A. IRB certification (in lieu of a copy of informed consent document)

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To:	Liana Castel, BA, MSPH
Department:	Epidemiology
Address:	CB #7435
Date:	December 22, 2005
From:	Suzanne L. West, PhD, Vice Chair Office of Human Research Ethics Public Health IRB
IRB Number:	05-2818
Title:	Dissertation: Longitudinal Epidemiology of Pain in Patients with Metastatic Breast Cancer
Subject:	Not human subjects research

As described in your application dated November 13, 2005, your protocol does not fit the definition of human subjects research as given in the Code of Federal Regulations, title 45, part 46.102(d) and (f), and is therefore not subject to IRB governance.

NOTE:
(1) This Committee complies with the requirements found in Part 56 of the 21 Code of Federal regulations and Part 46 of the 45 Code of Federal regulations. Federalwide Assurance Number: FWA-4801, IRB No. IRB00000540.

(2) Re-review of this proposal is necessary if any significant alterations or additions to the proposal are made

B. Brief Pain Inventory Instrument (Excerpts: severity and interference)

Intensity Items (4)

A. Please rate your pain by circling the one number that best describes your pain at its worst in the last 7 days:

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

B. Please rate your pain by circling the one number that best describes your pain at its least in the last 7 days:

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

C. Please rate your pain by circling the one number that best describes your pain on the average in the last 7 days:

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

D. Please rate your pain by circling the one number that tells how much pain you have right now:

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

Interference Items (7)

Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Permission: Data Usage – Novartis Pharmaceuticals Corporation

Subject: Email permission template
From: jens.grueger@novartis.com
Date: Thu, 3 Nov 2005 17:53:03 +0100
To: liana@unc.edu
CC: jeanfrancois.baladi@novartis.com

To: UNC School of Public Health Institutional Review Board
From: Jens Grueger, PhD, Global Head, Pricing & Health Economics, Novartis Parma AG, Basel

In my capacity as Global Head, Pricing & Health Economics at Novartis Pharma AG, with authority over the analysis datasets for two clinical trials (protocols numbered 4244603010 and 4244603039), I am writing to grant permission to Liana Castel to run her proposed analyses on these datasets for the purposes of her doctoral dissertation. This dataset contains no names or direct identifiers. Risk to patient confidentiality is minimized through the following:

1. Liana will comply with data protection procedures as required by all applicable human subjects regulations as outlined in the UNC IRB protocol for this study,

2. she will conduct the study in accordance with her dissertation proposal, and

3. the work produced from her analyses for the class (reports, tables, figures, abstracts, and manuscripts) will not contain PHI, only aggregate information.

Please feel free to contact me with any questions if further information is needed.

Jens Grueger, PhD
Global Head, Pricing & Health Economics
Novartis Pharma AG
Lichtstr.
CH-4002 Basel
T +41 61 324 5118
E-mail jens.grueger@novartis.com

Brief description of research:
The proposed research is a longitudinal analysis of clinical and demographic factors that affect pain trajectories as measured by the Brief Pain Inventory among breast and prostate cancer patients. The attached description justifies the importance of the research, outlines specific aims & overview of methods. With regards to the specific datasets I would like to use, they are from Novartis protocols numbered 4244603010 and 4244603039 with focus on panels BPAININV (pain), BASE (baseline info), DMG (demographics), PHASE (disease progression

and dropout), SRE (skeletal related events), and ANATYPE (analgesics). One very important thing I would like to specify is that there will be absolutely no treatment arm comparisons. The BPI would be the outcome studied, and as you recall, there were no differences in BPI scores over time by treatment arm in our previous analyses (a fact that makes adjustment for/ inclusion of treatment arm unnecessary for studyin! g pain trajecto! ries). All patients from all arms will therefore be grouped together for the analyses, since the goal would be to identify predictors of differences in pain trajectories. Variables I would like to examine as possible predictors would include demographics, skeletal-related events, treatments other than zometa or pamidronate that constituted standard of care, clinical events and characteristics such as date of bone metastases, and functional status. This would be very similar to the 10 FACT-trajectory study I helped conduct while at Duke; that was also NOT a treatment arm comparison: Weinfurt KP, Castel LD, Li Y, Timbie JW, Glendenning GA, Schulman KA (2004). Health-related quality of life among breast cancer patients receiving zoledronic acid or pamidronate disodium for metastatic bone lesions. Medical Care, 42:164-175. In light of my knowledge and experience working with Novartis over the past five years on other research with these data, I hope that yo! u will agree ! that the project entails extremely low risk to Novartis, and the benef it of offering generous goodwill and support to worthy academic research (at no additional monetary investment). I ask that permission can be granted as soon as possible so that I may proceed with my proposed dissertation plan.

D. Permission: BPI Data Analysis – M.D. Anderson Cancer Center

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

December 29, 2005

Liana D. Castel
Doctoral Candidate, Epidemiology
The University of North Carolina at Chapel Hill
Department of Epidemiology
2709 Buckboard Drive
Hillsborough, NC 27278

Dear Ms. Castel:

I am pleased that you have considered using the Brief Pain Inventory© (BPI) in your upcoming study. The study description you provided seems to be congruent with the intended use of the BPI. You may reproduce the BPI but your copyright use is limited only to this specific study. This permission extends to paper-and-pencil administration only, and does not extend to electronically administered formats. In addition, the following should appear in your reproduced copy.

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Additional information can be found by visiting our website: www.mdanderson.org/departments/prg

I look forward to having a summary of your results.

Sincerely,

Charles S. Cleeland, Ph.D.
McCullough Professor of Cancer Research
Chairman, Department of Symptom Research
Division of Internal Medicine

CSC:aps

cc: Tito R. Mendoza, Ph.D.

E. Permission: WHO Pain Ladder (Figure 4) – WHO

Subject: RE: Form: Request to Reproduce Copyright Material
From: "permissions" <permissions@who.int>
Date: Fri, 17 Mar 2006 11:33:08 +0100
To: <liana@unc.edu>

Dear Liana DesHarnais Castel,

Thank you for your enquiry. On behalf of the World Health Organization, we are pleased to grant you permission to reproduce the following WHO item, as indicated in your message below:

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WHO Pain relief ladder

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Below is the result of your feedback form. It was submitted by (liana@unc.edu) on Wednesday, March 15, 2006 at 03:42:53

FullName: Liana DesHarnais Castel

Organization: University of North Carolina at Chapel Hill

PostalAddress: 2709 Buckboard Drive
Hillsborough, NC 27278

OR alternatively:

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use: I would like to reproduce the WHO Pain Relief Ladder as part of my doctoral dissertation in Epidemiology. The title of my dissertation is LONGITUDINAL EPIDEMIOLOGY OF PAIN AMONG PATIENTS WITH METASTATIC BREAST CANCER. The reproduction of the ladder is part of the background section of my dissertation proposal, and I plan to reproduce it in the final dissertation that I will turn in to the UNC Graduate School. There is also a possibility, though remote, that a reproduction of the ladder would be included in manuscripts submitted for peer review in journals. Reproduction for that purpose is unlikely due to space limitations, however.

Where I do plan to reproduce the ladder in the dissertation, I would like to reproduce it with the following figure caption: "Figure X: Analgesic ladder for treatment of cancer pain. World Health Organization. Cancer pain relief and palliative care. Report of a WHO expert committee [World Health Organization Technical Report Series, 804]. 1-75. 1990. Geneva, World Health Organization." The accompanying text that is part of the background section of my dissertation describes the ladder and cites other works that reference it.

I hope that this explanation is clear. Please feel free to contact me with any questions by email at liana@unc.edu or by phone (United States number) at 919-643-2059.

Thank you very much for your time in considering my request. I hope to hear from you soon and can provide any further information you might need as part of the request. Best Regards, -Liana

---

F. Permission: Cancer Incidence (Figure 2) – American Cancer Society

American Cancer Society
1599 Clifton Rd., NE, Atlanta, GA 30329 404-417-5942 (Fax) www.cancer.org

May 5, 2006

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Date: 05/17/06

The American Cancer Society is the nationwide community- based voluntary health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives, and diminishing suffering from cancer, through research, education, advocacy, and service.

Exhibit A

The American Cancer Society is the nationwide community- based voluntary health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives, and diminishing suffering from cancer, through research, education, advocacy, and service.

Appendix F, continued (pg 4 of 4).

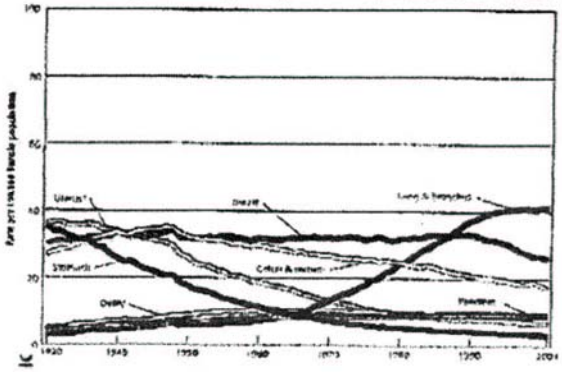
April 3, 2006

Excerpt from Liana Castel dissertation (this is how I would like to use the figure).

Incidence and mortality: breast cancer

Cancer incidence overall in the United States (source: National Cancer Institute) appears to have risen and is projected to rise in future years, especially among the elderly, rising in those aged 65 or older from incidence of approximately 1650 cases per million in 1974 to 2100 cases per million in 1996.[6] As shown in Figure 2 (age-adjusted cancer death rates in US females over the past 70 years), breast cancer is second only to lung cancer among the tumor types with highest mortality rates as of 2001. The present study's focus on breast cancer addresses an important tumor type.

Figure 2. Age-Adjusted Cancer Death Rates,* among Females by Tumor Site, US, 1930-2001



*Per 100,000, age-adjusted to the 2000 US standard population.
Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung & bronchus, colon & rectum, and ovary are affected by these coding changes. Source: American Cancer Society, Surveillance Research, 2005

Excerpt from Dssertation Reference List:

6 National Cancer Institute. SEER Cancer Statistics Review 1973-1996

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