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Predictors of patterns of pain, fatigue and insomnia during the first year following a cancer diagnosis in the elderly

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Abstract

Pain, fatigue and insomnia (PFI) are among the most prevalent, distressing, and under managed symptoms experienced by cancer patients. Research has demonstrated that PFI co-occur; what remains unclear are the patterning and stability of PFI patterns, and the patient, disease and treatment characteristics that predict PFI patterns over time. This secondary analysis used a dataset comprised of 867 elders (46% female) who were newly diagnosed with breast, colorectal, lung or prostate cancer and followed at four points during the year following diagnosis. The university's IRB approved this study. Descriptive statistics and multi-state transition models using multinomial logistic regression were employed. The typical participant was 72.6 years, reported 7.9 symptoms and 2.7 comorbidities. Prior PFI pattern was consistently associated with significantly increased risks for subsequent PFI pattern. At observations 1-3, lung cancer, treatment, higher comorbidity with breast cancer, and late stage colorectal cancer were significantly associated with increased risks for PFI patterns. Advancing age was not significantly associated with increased risks for PFI patterns. PFI co-occurrence declined over time, but was associated with significantly increased risks for death or loss to follow-up and increased reports of other symptoms. PFI co-occurrence is associated with adverse outcomes and should be proactively targeted for intervention.

INTRODUCTION

Elders are disproportionately affected by cancer; between 1996 and 1998, it was estimated that 1 in 3 males and 1 in 5 females between the ages of 60 and 79 years were diagnosed with cancer¹. The National Cancer Institute Surveillance Epidemiology, and End Results (SEER) Program data from 1994-1998 demonstrated that 60% of all malignant tumors occurred in persons aged 65 years or older. Therefore, it is plausible that of the estimated 1.44 million persons who will be diagnosed with cancer in 2007², over 860,000 of those diagnoses given will be to persons aged 65 years or older.

Symptoms and side effects arising from cancer and cancer treatment are a major problem and concern for cancer patients³. The adverse consequences of symptoms exert far reaching effects on many aspects of a cancer patient's life, including functional status, direct and indirect costs, roles, role responsibilities, quality of life, and length of survival⁴⁻¹¹, and these consequences may continue long after adjuvant therapy has ended and the patient has entered the survivorship phase^{12,13}. Complicating the cancer and treatment-related experience for elders is the fact that many are entering the cancer trajectory with other pre-existing co-morbidities,¹⁴ such as

diabetes, hypertension, or arthritis, all of which are associated with disease and treatment-related symptoms. Therefore, healthcare providers cannot assume that untoward effects reported by an elder cancer patient are solely attributable to their cancer experience, nor can healthcare providers assume that the cancer experience of an elder will mirror that of a younger adult.

The co-occurrence of PFI has been reported in the literature, with inter-correlations between pain, fatigue and insomnia ranging from weak to moderate.^{18-19,31} Samarel and colleagues²⁰ reported their fatigue plus insomnia factor showed a moderately strong correlation with a pain factor ($r = 0.42$). Pain interrupts nighttime sleep^{6,10,21,22}, and with pain control, sleep problems lessen²². Fatigue levels in the evening and in the morning were strongly correlated ($r \geq .7$) with sleep efficiency and total sleep time¹⁰. Pain, fatigue and insomnia (PFI) are particularly problematic for persons with cancer due to their prevalence and distress that is attributed to their presence^{5,8,9,15-17, 30}. PFI have been reported to occur in greater frequency in the presence of advanced stage disease^{3,10,41}, and overall greater symptom distress has been reported among patients with advanced stage disease^{3,5,41}.

Although research has demonstrated that PFI do co-occur, secondary to cancer and its treatment, what remains unclear is the patterning of PFI throughout the disease and treatment trajectory, the stability of these PFI patterns, and the patient, disease and treatment characteristics that predict PFI patterns over time. This study sought to address this gap in the knowledge through exploring the patient, disease and treatment characteristics that predict patterns of pain, fatigue and insomnia during the first year following a new cancer diagnosis.

METHODS

This study was a secondary analysis of the dataset *Home Care for Cancer—A Community-Based Model*, grant # R01 NR/CA01915, funded by the Department of Health and Human Services, the National Center for Nursing Research, the Agency for Healthcare Policy and Research, and the National Cancer Institute. The parent study was a descriptive, prospective, longitudinal study that examined the effects of sex, age, cancer site, stage of disease, and pre-existing co-morbid conditions on physical and mental health outcomes and symptoms in elders newly diagnosed with breast, colorectal, prostate, or lung cancer, as well as the effects of family caregiver assistance with symptom management and activities of daily living on both patient and family caregiver physical and mental health outcomes. This secondary analysis was approved for conduct by the university's institutional review board.

Subjects

The target population for the parent study included persons aged 65 years or older who were newly diagnosed with breast, colorectal, lung or prostate cancer. The rationale for limiting the cancer site to breast, colorectal, lung or prostate was that these are the four most frequently occurring types of cancer among persons in this age stratum. Using convenience sampling, participants were accrued from 24 communities in the Lower Peninsula of Michigan, excluding the Detroit Metropolitan area, and from one community in Indiana. Within these 24 communities, active recruitment occurred in 30 different treatment settings, including hospitals, oncology physician offices, and community cancer treatment centers.

Elders were eligible to participate if they were aged 65 or older; newly diagnosed with breast, colorectal, prostate or lung cancer; currently undergoing some form of treatment beyond palliation; spoke and read the English language; did not receive treatment in the previous 3 years for another cancer; and had a telephone. Patients were ineligible for participation in the study if they had hearing or cognitive deficits, such as dementia, or did not have a telephone. Inclusion criteria for these secondary analyses included subject sex, age, cancer site, and stage

of disease documented in the dataset. The parent study was a patient-caregiver dyad study, in which the patient identified a primary caregiver who would assist with care in the homes setting and the patients were not caregivers to an ill, elderly spouse. Identified caregivers were interviewed separate from the patient; the caregiver data are not presented in this paper. The parent study enrolled 1200 elder cancer patients. Nine hundred seventy six persons (81.33% of the parent study sample) met the eligibility criteria for this secondary analysis. One hundred-nine consented participants did not provide data at any data collection period. Of those 109 persons who consented to participate, but who did not provide any data, 34 participants (31%) were too ill, 12 participants (11%) could not be reached, 47 participants (43%) changed their mind and refused the study upon initial telephone contact, 11 participants (10%) had hearing deficits that precluded participation in a telephone interview, 4 participants (4%) only wished to have their caregiver participate in the study, and one participant (1%) died following consent but prior to their first (Wave 1) interview.

Procedures

Following informed consent, elders participated in telephone interviews at four points in time: 6-8 (Wave 1), 12-16 (Wave 2), 24 (Wave 3), and 52 (Wave 4) weeks following cancer diagnosis. Timing for the first and second interviews was linked to timing of receipt of radiation therapy or chemotherapy; timing for the last two interviews captured immediate post-treatment effects and sustained/decay effects secondary to disease and treatment. Retrospective medical record audits were conducted to verify site and stage of cancer, surgical procedure(s) performed, treatment(s) received.

Measures

Sociodemographic Questionnaire—This 10-item instrument asked participants to disclose social and demographic information, including but not limited to sex, date of birth, educational background, and marital status. Responses to all questions were closed ended and either came from a listed response set, or from a specific number or date provided by the participant. The principal investigators from the parent study developed the Sociodemographic Questionnaire.

Co-morbidity Index—This 15-item instrument is a self-report measure of pre- and co-existing co-morbid conditions with which the participant had been given a diagnosis from a health care professional. Response categories to these questions were both closed ended, with yes/no/do not know/refused or Likert scale options, or, as in the case of the final question, open ended, with the participant having the opportunity to report any health condition(s) that had not been identified through the instrument. This instrument is a condensed version of the larger *Aging and Health in America* instrument that was developed by the University of Michigan's Survey Research Center²³, for use in geriatric populations. The *Aging and Health in America* questionnaire was developed using a weighted sample of over 9000 older Americans of varied ethnicity and is a valid instrument for capturing self-reported health conditions in older Americans. Pre-existing comorbidity was captured through self-report, as prior research by Katz and colleagues⁴⁰ demonstrated an overall level of agreement between the medical record based audit their questionnaire exceeded 90%. Because only 7% (n = 65) of our sample reported no pre-existing health conditions, comorbidity was dichotomized into (0 - 3) or (4 or more) comorbid conditions for the purposes of modeling.

Patient Symptom Experience—This 37-item instrument is a self-report measure that asked participants if they had experienced any of the 37 listed symptoms during the previous two weeks, due to their cancer or cancer treatment. If participants answered affirmatively to any symptom, they were asked to rate the symptom's severity on a 3-point scale: mild, moderate, or severe. Participants were then asked to rate the extent to which the symptom

disrupted or caused them to limit their regular daily activities on a 5-point scale: no extent, small extent, some extent, great extent, or very great extent. This instrument was developed by Given and colleagues²⁴, was based on other symptom inventories used in cancer populations, such as the Symptom Distress Scale²⁵, and is a valid instrument for capturing symptom severity. The Cronbach's alpha coefficient for this instrument was 0.90²⁶.

Data Analysis

Descriptive statistics were run to describe the sub-sample's characteristics specific to sex, race, cancer site, cancer stage, co-morbid conditions, educational level, marital status, and living situation.

Our primary research question was: Do patient sex, age, comorbidity status, cancer site, stage of disease, or treatment regimen predict patterns of PFI over time? To address this we fit multi-state transition models using multinomial logistic regression. Multinomial logistic regression is used in circumstances in which the dependent variable is categorical and the categories do not have any particular rank-order; there is no restriction on the level of measurement of the predictor/independent variables²⁷. Based on symptom prevalence patterns we defined mutually exclusive and exhaustive symptom categories as (1) no PFI symptoms, (2) F only, (3) P, I or both without F, (4) F with one other symptom, and (5) all three symptoms.

Multinomial logistic regression (MLR) describes ratios of the risks for falling into each outcome category versus a reference category, comparing a particular regressor value versus a reference category (nominal regressors) or a contrast of one unit (continuous regressors). In our models, each PFI outcome category was compared to the "no PFI symptoms" (reference) category. Each category has its own unique linear prediction model, including intercept, α and vector of coefficients so that there is a distinct coefficient β_{ik} that corresponds to every regressor and category. MLR assumes linear relationships between the independent variables and the log ratios of outcome category prevalences.

At the first observation time, the selected variables for predicting symptom pattern prevalences were sex, age, co-morbidity category, treatment category, surgery status, cancer site and stage of disease. At the subsequent observation times, these variables, as well as the prior state PFI pattern that each elder reported were considered as current symptom pattern prevalence predictors. Diagnostics via the variance inflation factor (VIF) method were conducted at each observation time to determine whether the first-order predictor variables were highly correlated. A conservative rule for this determination is that no individual VIF score be greater than 10 and that the mean of all the VIFs is not considerably larger than 1²⁹. The mean VIF scores at each data collection point ranged from 1.76 - 1.83; at each observation time, none of the individual VIF scores exceeded 4.46.

Model building was conducted using likelihood ratio tests for hierarchically nested models and introduced a number of interaction terms to explore whether: 1) comorbidity category (0-3 versus 4 or more comorbid conditions) interacted with cancer site, cancer stage or treatment, and 2) cancer site interacted with stage of disease or sex, to predict PFI patterns at the 6 week data collection period. At subsequent observation times, the interaction of prior PFI state with comorbidity category was also tested. Analyses were conducted using STATA SE version 9²⁸. There were instances in which there were few (or no) individuals with combinations of covariates within outcome categories. With sparse cell sizes, interactions of interest could not be estimated, and in some cases, not even main effects; NA denotes such cases.

RESULTS

Sample Characteristics

Eight hundred sixty seven persons met the eligibility criteria and provided data to inform this secondary analysis. The typical participant was slightly older than 72 years, Caucasian, reported more than 2 pre-existing comorbid conditions, married and living with their spouse, and had attained a high school diploma or higher level of education. Fifty-four percent of this subset ($n = 465$) was male and 46% ($n = 402$) was female. The cancer site composition of this subset included prostate ($n = 285$, 29%), breast ($n = 234$, 27%), lung ($n = 221$, 24%), and colorectal cancer ($n = 153$, 18%); 593 (68%) were diagnosed with early stage disease and 274 (32%) were diagnosed with late stage disease. Table 1 provides the sociodemographic data for the elders (see Table 1).

The top five most frequently reported comorbid conditions included: 1) hypertension (50.3%, $n = 406$), 2) heart problems (31%, $n = 250$), 3) hearing deficit (24.9%, $n = 201$), 4) vision deficit (23.2%, $n = 187$), and 5) arthritis (20.5%, $n = 166$).

At Wave 1, 846 elders (98%) completed interviews; subsequently the numbers were 723 (83%) at Wave 2; 664 (77%) at Wave 3; and 592 (68%) at Wave 4. Five hundred eighteen elders (60%) completed all four interviews. Statistical tests were conducted to explore whether sociodemographic or physical characteristics of the study sample were associated with completing versus not completing the four waves of data collection. Completing all four interviews was associated with being female (χ^2 (1 d.f.) = 9.857, $p = .002$), with being diagnosed with breast, colorectal or prostate cancer in comparison to lung cancer (χ^2 (3 d.f.) = 88.133, $p = .000$), with having early stage disease (χ^2 (1 d.f.) = 72.099, $p = .000$), with being younger ($F = 4.313$, $p = .038$), with being Caucasian (χ^2 (3 d.f.) = 8.566, $p = .036$), and with having a high school diploma or higher level of education (χ^2 (6 d.f.) = 42.429, $p = .000$). There was no association between completing all four waves of data collection and co-morbidity category (χ^2 (1 d.f.) = 1.055, $p = .304$), marital status (χ^2 (3 d.f.) = 1.296, $p = .730$), or living situation (χ^2 (2 d.f.) = .822, $p = .663$).

Study subjects received a variety of treatments for their cancers, including surgical excision of the tumor ($n = 667$, 68%), and/or chemotherapy alone ($n = 93$, 9.5%), radiation therapy alone ($n = 328$, 33.6%), or chemotherapy with radiation therapy ($n = 129$, 13.2%). There was no association between completing all four waves of data collection and treatment category (no adjuvant therapy, chemotherapy alone, radiation therapy alone, chemotherapy + radiation therapy) (χ^2 (3 d.f.) = 4.027, $p = 0.260$). There was an association between having surgery and completing all four waves of data collection (χ^2 (1 d.f.) = 71.789, $p = .000$); however, a majority of the study subjects underwent surgery and completed all four waves of data collection.

Symptom prevalence shifts and interrelationships over time

PFI pattern prevalences shifted over time following cancer diagnosis. The prevalence of PFI co-occurrence peaked at Wave 1 (6-8 weeks after cancer diagnosis), with 18% ($n = 152$) of the elders reporting PFI co-occurrence (see Table 2). At each subsequent Wave of data collection, PFI co-occurrence steadily decreased such that by Wave 4 (one year post diagnosis), 6% ($n = 35$) of the elders reported PFI co-occurrence. Conversely, reports of *no* PFI were at their lowest at Wave 1, with 18% ($n = 155$) of the elders reporting *no* PFI. Over time, an inverse trend was noted between PFI co-occurrence and *no* PFI; by Wave 4, 43% ($n = 256$) of the elders reported *no* PFI, although 336 (57%) reported at least one of these symptoms.

Pain, fatigue and insomnia did not have high intercorrelations for any wave of data collection. Wave 1 correlations for PFI included: PI ($r = 0.20$), FI ($r = 0.15$), and FP ($r = 0.20$). PFI correlations for subsequent waves were very similar. These intercorrelations were higher than

those found by Dodd and colleagues¹⁸, but lower than those reported by Beck and colleagues.³¹

PFI Predictors at Wave 1

The final model for predicting PFI patterns at the Wave 1 observation period included patient sex, comorbidity status, cancer site, stage of disease, treatment modality, surgery and the interaction of comorbidity x cancer site. Likelihood ratio testing indicated the interaction terms comorbidity x treatment, comorbidity x stage, cancer site x stage, and cancer site x sex were not significant, thus they were not included in the final model. Age was not associated with significant risks for any of the PFI patterns (likelihood ratio χ^2 (4 d.f.) = 5.54, $p = 0.236$) and was not included in the final model. Table 3 displays the relative risk ratios (RRRs) and 95% confidence intervals (CIs) for each predictor variable, by PFI pattern, for the Wave 1 observation period (see Table 3).

PFI Predictors at Wave 2

The final model for predicting the Wave 2 PFI patterns included patient sex, comorbidity status (0-3 versus 4 or more comorbid conditions), cancer site, stage of disease, treatment modality, prior PFI state, and the interaction of cancer site x stage. Likelihood ratio testing indicated that comorbidity x treatment, comorbidity x cancer site, comorbidity x stage, comorbidity x prior PFI state, and cancer site x sex were not significant predictors, thus they were not included in the final model. In addition, age was excluded from the final model because it was not associated with significant risks for any of the PFI patterns (likelihood ratio χ^2 (4 d.f.) = 5.37, $p = 0.252$). Table 4 displays the RRR's and 95% CIs of the predictor variables (see Table 3). Noteworthy in Table 4 are the NA's in the outcome categories a) fatigue + insomnia or fatigue + pain, and b) PFI co-occurrence for the interaction term stage x breast cancer. These statistics owe to the result that none of the late stage breast cancer patients reported either of the outcomes at issue at Wave 2.

PFI Predictors at Wave 3

The final model for predicting the Wave 3 PFI patterns included patient sex, comorbidity status (0-3 versus 4 or more comorbid conditions), cancer site, stage of disease, treatment modality, and prior PFI state. Likelihood ratio testing indicated that comorbidity x treatment, comorbidity x cancer site, comorbidity x stage, comorbidity x prior PFI state, cancer site x stage and cancer site x sex were not significant predictors, thus they were not included in the final model. As for Waves 1 and 2, age was also excluded; it was not associated with significant risks for any of the PFI patterns (likelihood ratio χ^2 (4 d.f.) = 8.13, $p = 0.087$). Table 5 displays the RRR's and 95% CIs of the predictor variables (see Table 5).

PFI Predictors at Wave 4

The initial model for predicting the Wave 4 PFI patterns included patient sex, comorbidity status (0 - 3 versus 4 or more comorbid conditions), cancer site, stage of disease, treatment, surgery, prior PFI state, the interaction of comorbidity x prior PFI state, the interaction of cancer site x stage and the interaction of cancer site x sex. Age was not associated with significantly increased risk for any of the PFI patterns at Wave 4, and thus, was omitted (likelihood ratio χ^2 (4 d.f.) = 2.70, $p = 0.61$).

It was noted that the comorbidity x prior PFI state interaction terms were associated with clinically meaningless RRR's for Wave 4 PFI patterns, and many of the 95% CIs for these comorbidity x prior PFI pattern interaction terms were undefined. For example, in the outcome category fatigue + insomnia or fatigue + pain, the association between higher comorbidity and reporting FI or FP at Wave 4 was reduced by 93% in the presence of fatigue at Wave 3. Even

though this is a statistically significant finding, we suspected it to be an artifact of model overfit due to cell-sizes for comorbidity x prior PFI state x PFI pattern at Wave 4. In fact, a cross-tabulation of Wave 4 PFI patterns x comorbidity x prior PFI state at Wave 3 included three cells that contained a zero value. The decision was made to omit the comorbidity x prior PFI state interaction terms from the final Wave 4 model. Additionally, there were only 35 individuals who reported PFI co-occurrence at the Wave 4 observation; clearly, the statistical model overfit the available data. The decision was made to omit the PFI outcome category from the Wave 4 final model.

The final Wave 4 model for predicting PFI patterns included the variables sex, comorbidity, cancer site, stage of disease, treatment, surgery, the Wave 3 PFI state, and the interaction terms cancer site x stage and sex x lung cancer. Table 6 provides a display of the RRR's and 95% CIs for each of the predictor variables (see Table 6).

Finally, we also considered other symptoms that may have contributed to PFI patterns, but were not included in the primary analyses. Table 7 displays the mean number of other symptoms that patients reported, by PFI pattern, by wave of data collection (see Table 7). Participants who did not report PFI at any wave, reported, on average, 3 other symptoms. As participants reported various PFI patterns, the mean number of other symptoms reported ranged from 4 to more than 9 (across all PFI patterns, across all waves of data collection). Thus, elder cancer patients who experience pain, fatigue, and/or insomnia throughout their cancer and treatment trajectories may be susceptible to experiencing many other symptoms.

Attrition and its predictors over time

Two hundred-fifty five cases (29%) provided data for only the Wave 1 observation. In an effort to understand how PFI patterns, as well as other variables of interest predicted attrition at the subsequent observations, post-hoc analyses were conducted. Eighty-eight of the elders, who met eligibility criteria for this secondary analysis, died while participating in the parent study; one of the elders died following consent, but prior to participating in the first data collection. In addition, 167 elders were lost to follow-up, but did not die, following completion of the Wave 1 data collection.

At the Wave 2 observation, 15 elders had died and 108 elders were LTF. Significant predictors for death at Wave 2 included having a diagnosis of colorectal or lung cancer, having late stage disease, receiving chemotherapy, and reporting PFI at Wave 1. Significant predictors for LTF at Wave 2 included having a diagnosis of lung cancer, having late stage disease, receiving chemotherapy or radiation therapy (alone or in combination), and reporting the PFI patterns of FI or FP, or PFI at Wave 1.

At the Wave 3 observation, an additional 38 elders had died and 21 elders were LTF. Significant predictors for death at Wave 3 included having a diagnosis of lung cancer, having late stage disease, and reporting the PFI patterns of FI or FP, or PFI at Wave 2. Significant predictors for LTF at Wave 3 included having a diagnosis of lung cancer, and reporting the PFI patterns of P, I or PI, or PFI at Wave 2.

At the Wave 4 observation, an additional 34 elders had died and 38 elders were LTF. Significant predictors for death at Wave 4 included having 4 or more comorbid conditions, having a diagnosis of lung cancer, having late stage disease, and reporting the PFI patterns of P, I or PI; FI or FP; or PFI at Wave 3. Significant predictors for LTF at Wave 4 included a diagnosis of lung cancer, and reporting the PFI patterns FI or FP, or PFI at Wave 3.

Limitations

There are limitations to this study that merit discussion. The parent study used convenience sampling, and although convenience sampling is an efficient and cost-effective means for accruing a study sample, its limitations are acknowledged. Specifically, self-selection into any research endeavor may impose extraneous characteristics that, while not part of the study, may influence the analyses due to influence of, or relatedness to, the outcome of interest.

Data were not gathered on those individuals who met eligibility for participation, but declined to participate. Therefore, comparisons cannot be made on variables of interest, such as patient age, sex, or race; site of cancer or stage of disease; or pre-existing comorbidity to explore possible predictors for non-participation. It seems plausible that eligible persons who had many symptoms would decline participation. Additionally, subjects were excluded from the study if they did not have a telephone, could not hear normal conversation, or did not speak and understand the English language. It is unclear the extent to which these excluded persons differed from those who fully met the eligibility requirements for participation, as there were no demographic data gathered from those individuals who were excluded, from which comparisons could be made.

In spite of the multiple sites used for recruitment, the sample was racially homogeneous, with the sample being comprised of Caucasian (n = 806, 93%), African American (n = 55, 6%), Latino (n = 2, < 1%), and Native American (n = 4, < 1%) elders. Because of the lack of racial variability in this sample, it was impossible to make any PFI patterning comparisons by race.

With the exception of data directly related to the participants' cancers (site, stage, adjuvant therapy), the data for this secondary analysis were obtained through self-report/participant interviews. Although the work of Katz and colleagues⁴⁰ demonstrated a high level of agreement between self-report of comorbidity and medical record audit, we do acknowledge that persons may over- or under-report health conditions.

Whether or not these elder cancer patients were receiving adjuvant medications, such as anti-anxiety, analgesics, anti-depressants, anti-emetics, hypnotics, erythropoiesis-stimulating agents, or growth-stimulating factors was not available in the data set. Thus, while we acknowledge that adjuvant medications clearly would affect the participants' symptom experiences, for the purposes of this secondary analysis, we were unable to address the effects of adjuvant medications on our outcomes of interest.

Retention of participants in longitudinal studies is a challenge and we acknowledge the effects of attrition from the study. We have previously addressed the issue of attrition from this study and the relationships between our outcomes of interest and participant death or loss to follow-up. Attrition from this study imposes a threat to the external validity of this study.

Discussion

This secondary analysis found that advancing age was not significantly associated with increased risks for patterns of PFI. The Helme and Gibson³² review on the epidemiology of pain in elders reported that after the seventh decade of life, reports of pain in the elderly decline. This decrease in pain reporting may be attributable to age-related changes in nociceptive functioning, specifically peripheral and central nervous system pathways.³² Sex was associated with significant risks for reporting FI or FP at the Wave 3 observation, and for reporting fatigue at Wave 4, such that being female carried a 2.5 RRR and 3.21 RRR, respectively, for reporting these patterns when compared to males. Research that explored sex differences in pain, fatigue and insomnia as isolated symptoms in cancer patients is minimal. In spite of this paucity, research has shown no sex differences in reports of average, worst or

least pain intensity scores³³, and that females report greater levels of fatigue and sleep disturbance³⁴.

Comorbidity was a prevailing issue among this sample of elders, with only 7% (n = 65) reporting *no* pre-existing comorbid conditions. The typical elder reported more than 2 comorbid conditions, and 27% (n = 236) reported 4 or more comorbid conditions. Thirty-one percent of the elders reported being told by a health care professional that they had heart problems, 20% reported being told they had arthritis, 50% reported high blood pressure, and just fewer than 16% reported being told they had a chronic lung disease. Having 4 or more comorbid conditions was associated with a 2-fold increased RRR for reporting fatigue at Wave 1. Increased comorbidity in the presence of breast cancer was associated with 4-fold and 7-fold increased RRRs for reporting the pattern FI or FP, or the pattern PFI, respectively, at Wave 1. It is curious that comorbidity as either a first order term, or an interaction term, was not a significant predictor for PFI patterns at Waves 2 or 3.

Treatment modality (single and multi-modal) was associated with significantly increased risks for PFI patterns at Waves 1, 2 and 3, coinciding with initial phase, mid-point, and completion of adjuvant therapy, respectively. Thus, we were able to observe for immediate and accumulative effects from cancer treatment. Of note, the greatest impact of treatment on predicting PFI patterning was noted at the Wave 2 observation. At the Wave 4 observation, which was scheduled at 52 weeks after diagnosis, treatment modality was no longer significantly associated with increased risks for reporting PFI patterns.

Table 2 highlighted the fluid nature of PFI patterns over time, namely that the participants' reports of PFI co-occurrence lessened over time, with movement towards no reports of PFI. Though of interest, there were some elders who moved from reporting F or, P I or PI at one observation, to reporting FI or FP, or PFI at the subsequent observation. In spite of these findings, a moderate proportion of this sample reported problems with ongoing pain (25.2%), fatigue (40.4%) and insomnia (23.2%) one year following their cancer diagnosis.

Thirty-percent of the elders who consented to participate in the parent study, did not complete the study. One hundred nine elders withdrew from the study upon initial contact for the Wave 1 interview. Among those elders who were included in this secondary analysis and completed the first Wave of data collection, 88 elders died and an additional 167 elders withdrew from the study at subsequent data collections. Having a lung cancer diagnosis, having late stage disease, and reporting PFI at a prior observation were each significantly associated with death at the Waves 2, 3 and 4 observations. Being diagnosed with lung cancer and reporting PFI at a prior observation were significantly associated with being LTF, at the Wave 2, 3 and 4 observations. Since an outcome of interest, PFI co-occurrence, was significantly associated with attrition at Waves 2, 3, and 4, our remaining sample for these Waves of analysis may have been biased such that variables not shown to be statistically significant predictors of PFI patterns *may* be predictive of increased RRRs for PFI patterning. In addition, this study did not explore the contribution of other symptoms in predicting either PFI patterns or attrition, yet further analyses demonstrated that elders who reported PFI co-occurrence at any observation also reported, on average, 9 other symptoms.

It is apparent that there exists an association between PFI patterns and the number of other symptoms being reported, but causal direction cannot be asserted through the results from this secondary analysis. What are not yet fully appreciated are the mechanisms through which PFI patterns occur over time. This study explored the patient, disease and treatment predictors of PFI patterns, but was not able to explore how biological/immunological mechanisms may have impacted PFI patterning. Past work has suggested a relationship between cancer and treatment-related symptoms and pro-inflammatory cytokines.^{15, 35,36}

The bi-directional association between pain (acute or chronic) and sleep disturbance is well articulated.^{37,38} A recent study involving healthy volunteers reported that restricted sleep was significantly associated with increased IL-6 levels and subsequent increases in complaint of bodily pain and fatigue/tiredness,³⁹ providing further evidence that pain, fatigue and insomnia may have a biological link.

Cancer survivors often seek their post-treatment health care needs through primary care providers, who may or may not be familiar with the long-term effects of cancer and/or its treatment. An additional issue that must be addressed is that of advancing age and the degree to which cancer and treatment-related symptoms in the elderly may not be sufficiently managed. We must question whether this insufficient management stems from a belief that cancer and treatment-related symptoms are a normative experience in the elderly. Again, the results of this study do not elucidate why these elders had unmanaged or under managed symptoms throughout the study, only that they reported symptoms throughout the first year following their cancer diagnosis.

Research Implications

In spite of what this study demonstrated regarding the patterning of pain, fatigue and insomnia, there are numerous gaps in the state of our knowledge of these three cardinal symptoms in cancer. Additional research is needed to explore: 1) whether there are sex differences in pain, fatigue and insomnia patterning; 2) whether there are moderating effects among pain, fatigue and insomnia, such that in the presence of any two or all three of these symptoms, a synergistic effect occurs to attract other symptoms; 3) whether a biological or immunological link exists among pain, fatigue and insomnia; 4) the time-ordered nature of pain, fatigue and insomnia presentation in cancer patients, specifically does one symptom “drive” the appearance of the others; 5) how pre-existing pain, fatigue and insomnia may impact disease progression and response to cancer treatment; and 6) the impact of intervening on pain, fatigue and insomnia on other symptom reports.

Practice Implications

Symptom management is an issue and priority in all oncology settings, regardless of the patient's age, site of cancer or treatment protocol. Nursing is in a pivotal role to facilitate symptom management for elderly cancer patients through: 1) ongoing assessment for cancer and treatment-related symptoms, including severity and impacts on usual daily activities and functional ability, and 2) ongoing assessment of the effectiveness of symptom management strategies implemented by the elder cancer patient or their family caregiver. In the event that the symptom management strategies employed have been ineffective, the nurse can suggest alternative symptom management strategies and should provide parameters to the elder cancer patient and their family caregiver for involving the health care system (nurses, physicians). In the event that family caregivers are not involved in symptom management, the nurse should assess the willingness of the family caregiver to provide assistance when it is needed, as well as the willingness of the elder cancer patient to ask for assistance when it is needed and accept assistance when/if it is offered.

Summary

Cancer and treatment related symptoms rarely occur in isolation. Among the many symptoms that a person diagnosed with cancer may experience, pain, fatigue and insomnia are, perhaps, the most prevalent and problematic cancer and treatment related symptoms. Pain, fatigue and insomnia may be particularly problematic among elder cancer patients; pre-existing co-morbidity and/or age-related changes in sleep architecture and continuity, may predispose elder cancer patients to increased risks for PFI patterns throughout the cancer and treatment

trajectories, as well as into the post-treatment phase. This study provided evidence that prior PFI patterns were significantly associated with increased RRRs for ongoing PFI and even death, and PFI patterns were associated with increased reports of other symptoms. A moderate proportion of our elders continued to experience PFI patterns up to one year following their cancer diagnosis. Thus, interventions targeted toward the amelioration of pain, fatigue and insomnia have the potential to reduce the adverse consequences that elders may experience secondary to pain, fatigue and insomnia and improve quality of life.

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Table 1

Sample characteristics (n = 867)

	n(%)	<u>X</u> (s.d.)
Sex		
Male	465 (54)	
Female	402 (46)	
Age		72.6 (5.3), range 64 - 98
Cancer Site		
Prostate	285 (29)	
Breast	234 (27)	
Lung	224 (26)	
Colorectal	153 (18)	
Stage		
Early	593 (68)	
Late	274 (32)	
Comorbidity		2.7 (1.7), range 0 - 9
0 - 3	572 (66)	
4 or more	236 (27)	
Missing	59 (7)	
Race		
Caucasian	806 (93)	
African American	55 (6)	
Latino	2 (<1)	
Native American	4 (<1)	
Marital Status		
Single	23 (3)	
Married	568 (66)	
Divorced/Separated	56 (6)	
Widowed	214 (25)	
No response/refused	6 (<1)	
Living Situation		
Alone	194 (20)	
With spouse	559 (57)	
With other(s)	95 (10)	
No response	9 (<1)	
Missing	16 (13)	
Education (highest level)		
No formal education	3 (<1)	
Grade School	68 (8)	
Some High School	177 (20)	
Diploma	263 (31)	
Some College	189 (22)	

	n(%)	<u>X</u> (s.d.)
College Graduate	83 (10)	
Graduate Degree	53 (6)	
No response/refused	14 (1)	
Missing	17 (2)	

Table 2
Frequencies of pain, fatigue and insomnia (PFI) patterns, by wave of data collection

	None	F	P, I or PI	FI or FP	PFI
Wave 1 (n = 846)	155 (18%)	168 (20%)	145 (17%)	226 (27%)	152 (18%)
Wave 2 (n = 723)	195 (27%)	152 (21%)	122 (17%)	161 (22%)	93 (13%)
Wave 3 (n = 664)	237 (36%)	140 (21%)	111 (17%)	119 (18%)	57 (8%)
Wave 4 (n = 592)	256 (43%)	104 (18%)	98 (16%)	99 (17%)	35 (6%)

Table 3

Personal, physical and treatment predictors of patterns of pain, fatigue and insomnia (PFI) at the Wave 1 data collection point, relative risk ratios (RRR) and 95% confidence intervals (CI)

	fatigue*		pain, insomnia, or both*		Fatigue + insomnia fatigue + pain*		pain, fatigue and insomnia*	
	RRR	95% CI	RRR	95% CI	RRR	95% CI	RRR	95% CI
Sex	2.03	0.84 - 4.88	1.28	0.51 - 3.20	1.15	0.50 - 2.65	1.84	0.77 - 4.37
Comorbidity	2.22	1.00 - 4.94	0.78	0.32-1.88	1.20	0.51 - 2.83	1.00	0.29 - 3.47
Breast**	1.06	0.33 - 3.35	0.65	0.20 - 2.10	1.51	0.51 - 4.48	1.11	0.33 - 3.72
Colorectal**	1.83	0.68 - 4.92	1.09	0.43 - 2.75	2.30	0.95 - 5.61	2.25	0.82 - 6.17
Lung**	2.90	1.04 - 8.07	2.15	0.80 - 5.79	6.74	2.67 - 17.04	8.41	2.97 - 23.80
Stage	1.03	0.57 - 1.87	1.11	0.61 - 2.02	0.94	0.53 - 1.66	1.62	0.88 - 3.00
Chemo + Radiation	2.49	1.09 - 5.70	0.69	0.28 - 1.69	0.89	0.40 - 1.97	0.65	0.27 - 1.57
Chemotherapy	1.91	0.78 - 4.68	1.09	0.45 - 2.66	0.82	0.35 - 1.92	0.60	0.23 - 1.55
Radiation	1.49	0.80 - 2.77	0.40	0.21 - 0.75	0.52	0.30 - 0.93	0.45	0.24 - 0.86
Surgery	0.89	0.47 - 1.70	0.70	0.36 - 1.37	0.82	0.44 - 1.54	1.77	0.85 - 3.65
Comorbid X Breast	0.56	0.11 - 2.81	4.16	0.86 - 20.20	4.69	1.11 - 19.76	7.47	1.32 - 42.31
Comorbid X CRC	1.02	0.19 - 5.46	1.30	0.20 - 8.42	2.08	0.40 - 10.83	0.83	0.10 - 7.08
Comorbid X Lung	0.71	0.15 - 3.42	1.23	0.23 - 6.65	1.04	0.22 - 4.88	2.91	0.48 - 17.59

Note: Bolded RRRs and 95% CIs indicate statistical significance

* no reports of P, F or I is the reference category

** Prostate is the reference

Table 4

Personal, physical and treatment predictors of patterns of pain, fatigue and insomnia (PFI) at the Wave 2 data collection point, relative risk ratios (RRR) and 95% confidence intervals (CI)

	fatigue*		pain, insomnia, or both*		fatigue + insomnia fatigue + pain*		pain, fatigue and insomnia*	
	RRR	95% CI	RRR	95% CI	RRR	95% CI	RRR	95% CI
Sex	1.06	0.46 - 2.42	0.90	0.37 - 2.21	1.60	0.69 - 3.71	1.93	0.77 - 4.87
Comorbidity	1.08	0.62 - 1.87	0.82	0.45 - 1.48	1.55	0.90 - 2.67	0.91	0.47 - 1.78
Breast	1.17	0.38 - 3.64	1.50	0.46 - 4.83	1.32	0.41 - 4.19	2.64	0.58 - 11.92
Colorectal	1.30	0.48 - 3.50	0.51	0.16 - 1.67	0.59	0.19 - 1.84	2.12	0.47 - 9.49
Lung	1.37	0.45 - 4.15	2.11	0.75 - 5.91	1.34	0.45 - 3.97	7.68	1.94 - 30.32
Stage	1.40	0.55 - 3.58	0.46	0.14 - 1.55	0.57	0.17 - 1.94	1.60	0.30 - 8.41
Chemo + Radiation	2.28	0.96 - 5.39	2.55	1.04 - 6.23	2.76	1.15 - 6.65	2.35	0.84 - 6.60
Chemotherapy	4.79	1.91 - 12.04	2.02	0.70 - 5.81	4.04	1.51 - 10.81	2.86	0.86 - 9.53
Radiation	2.47	1.28 - 4.79	2.70	1.37 - 5.33	3.33	1.67 - 6.63	4.93	2.19 - 11.13
Surgery	0.88	0.43 - 1.77	1.19	0.57 - 2.48	0.60	0.29 - 1.24	1.30	0.52 - 3.21
F I	4.24	2.18 - 8.23	2.09	0.93 - 4.69	6.66	2.66 - 16.69	5.03	0.93 - 27.20
P, I or PI I	0.74	0.32 - 1.73	3.66	1.75 - 7.66	3.63	1.37 - 9.61	7.49	1.44 - 38.79
FI or FP I	5.67	2.66 - 12.08	7.04	3.12 - 15.89	30.94	12.10 - 79.09	56.75	11.89 - 270.86
PFI I	5.39	2.12 - 13.68	5.59	2.03 - 15.44	40.78	14.17 - 117.36	107.62	21.20 - 546.38
Stage x Breast	1.08	0.17 - 6.87	1.77	0.20 - 15.92	NA		NA	
Stage x CRC	2.45	0.53 - 11.35	12.74	1.99 - 81.58	13.17	2.19 - 79.37	1.51	0.15 - 15.27
Stage x Lung	0.80	0.16 - 4.10	2.45	0.42 - 14.21	2.70	0.47 - 15.3807	0.83	0.10 - 6.82

Note: Bolded RRRs and 95% CIs indicate statistical significance

* No reports of P, F or I is the reference category

Table 5

Personal, physical and treatment predictors of patterns of pain, fatigue and insomnia (PFI) at the Wave 3 data collection point, relative risk ratios (RRR) and 95% confidence intervals (CI)

	fatigue*		pain, insomnia, or both*		fatigue + insomnia* pain		pain, fatigue and insomnia*	
	RRR	95% CI	RRR	95% CI	RRR	95% CI	RRR	95% CI
Sex	1.03	0.46-2.31	1.26	0.49-3.25	2.58	1.06-6.24	2.03	0.64-6.41
Comorbidity	1.13	0.66-1.93	1.12	0.63-2.00	1.27	0.72-2.26	1.39	0.65-2.96
Breast	1.70	0.58-5.00	0.80	0.24-2.65	0.69	0.21-2.30	3.91	0.65-23.60
Colorectal	1.38	0.58-3.30	0.64	0.24-1.73	0.76	0.26-2.23	1.17	0.20-6.84
Lung	2.02	0.85-4.78	0.98	0.39-2.47	1.74	0.66-4.60	3.55	0.81-15.57
Stage	1.81	1.00-3.27	1.36	0.69-2.68	1.66	0.85-3.25	3.76	1.48-9.54
Chemo + Radiation	1.83	0.80-4.20	1.41	0.55-3.59	1.85	0.74-4.62	1.03	0.30-3.54
Chemotherapy	1.13	0.47-2.73	0.84	0.28-2.54	2.49	1.01-6.15	2.00	0.64-6.27
Radiation	0.72	0.38-1.36	0.77	0.40-1.49	1.07	0.54-2.12	0.65	0.26-1.66
Surgery	0.80	0.40-1.59	1.02	0.49-2.11	1.69	0.77-3.73	0.83	0.27-2.60
F 2	3.39	1.86-6.17	0.72	0.29-1.83	3.84	1.70-8.68	5.09	1.21-21.44
P, I or PI 2	0.96	0.42-2.21	4.64	2.38-9.03	3.98	1.66-9.50	3.11	0.58-16.82
FI or FP 2	4.15	2.05-8.42	5.50	2.63-11.53	12.24	5.33-28.12	23.24	5.97-90.50
PFI 2	3.95	1.24-12.58	7.44	2.39-23.11	25.35	8.25-77.83	96.25	20.72-447.11

Notes: Bolded RRR's and 95% CI's indicate statistical significance

* = No pain, fatigue or insomnia is reference category

Table 6

Personal, physical and treatment predictors of patterns of pain, fatigue and insomnia at the Wave 4 data collection point, relative risk ratios (RRR) and 95% confidence intervals (CI)

	fatigue*		pain, insomnia, or both*		fatigue + insomnia fatigue + pain*	
	RRR	95% CI	RRR	95% CI	RRR	95% CI
Sex	3.21	1.02 - 10.08	2.03	0.53 - 7.79	2.74	0.72 - 10.39
Comorbidity	1.31	0.74 - 2.34	1.49	0.81 - 2.75	1.56	0.85 - 2.87
Breast	0.55	0.14 - 2.26	0.66	0.14 - 3.13	0.93	0.19 - 4.64
Colorectal	1.06	0.31 - 3.63	0.50	0.12 - 2.02	0.88	0.20 - 3.86
Lung	5.38	1.27 - 22.75	6.90	1.74 - 27.34	16.50	4.11 - 66.30
Stage	0.99	0.29 - 3.40	0.85	0.24 - 3.04	2.57	0.76 - 8.64
Chemo + Radiation	0.68	0.25 - 1.82	1.96	0.81 - 4.72	1.11	0.44 - 2.79
Chemotherapy	1.15	0.45 - 2.89	0.88	0.30 - 2.56	0.69	0.24 - 1.97
Radiation	1.71	0.88 - 3.32	1.28	0.64 - 2.56	1.08	0.52 - 2.22
Surgery	1.08	0.50 - 2.36	2.21	0.95 - 5.12	0.87	0.38 - 1.99
F 3	4.81	2.56 - 9.02	0.80	0.29 - 2.18	4.42	1.93 - 10.10
P, I or PI 3	1.92	0.89 - 4.16	5.50	2.78 - 10.88	4.16	1.76 - 9.81
FI or FP 3	2.37	0.96 - 5.86	6.20	2.77 - 13.89	16.05	6.88 - 37.46
PFI 3	6.67	1.76 - 25.25	6.58	1.65 - 26.28	25.89	7.14 - 93.90
Stage x Breast	0.34	0.04 - 2.80	0.36	0.03 - 4.98	NA	
Stage x CRC	1.17	0.21 - 6.41	2.64	0.41 - 16.94	0.74	0.12 - 4.48
Stage x Lung	1.02	0.14 - 7.70	0.76	0.09 - 6.27	0.16	0.02 - 1.11
Sex x Lung	0.06	0.01 - 0.42	0.09	0.01 - 0.70	0.08	0.01 - 0.57

Notes: Bolded RRR's and 95% CI's indicate statistical significance

* = No pain, fatigue or insomnia is reference category

Other symptoms reported, mean (s.d.), by pain, fatigue, and insomnia (PFI) pattern, by wave of data collection

Table 7

	None	F	P, I or PI	FI or FP	PFI
Wave 1	3.6 (2.5)	5.4 (3.3)	5.6 (2.9)	7.7 (3.9)	9.6 (3.8)
Wave 2	2.9 (2.1)	5.6 (3.2)	5.4 (2.7)	7.8 (3.8)	8.9 (3.8)
Wave 3	2.8 (2.3)	5.0 (3.2)	4.8 (2.7)	7.4 (3.5)	9.3 (3.9)
Wave 4	2.5 (2.2)	5.0 (3.5)	4.2 (2.9)	7.0 (3.6)	9.7 (4.3)