AGE DIFFERENCES IN THE EXPERIENCE OF CANCER PAIN

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ABSTRACT

The aim of this dissertation is to elucidate age-related patterns in the multidimensional experience of cancer pain. Chapter 1 presents a literature review of age-related patterns in cancer pain, outlines the methodological limitations of existing literature and highlights gaps in our knowledge. Chapter 2 presents the first psychometric analysis of the Short-Form McGill Pain Questionnaire-2 in older and younger people with cancer pain. The weight of the evidence suggests that this tool is valid for use in older and younger people with cancer pain. Chapter 3 presents an analysis of age-related patterns in the experience of cancer pain across the biopsychosocial spectrum. Pain intensity, qualities, and interference did not differ across age groups but older patients were somewhat less likely to be prescribed an opioid. Comorbidity was associated with greater pain for younger, but not older people, and chronic nonmalignant pain was associated with greater pain for older, but not younger people. An age-related pattern in the supportive context of cancer pain based on health status factors may also be present. There were no age differences in depressive symptoms, but intrusive thoughts were associated with greater pain for younger but not older patients, suggesting a unique adaptive advantage of prior experience with health limitations among older, but not younger patients. Chapter 4 presents a preliminary investigation of the role of pain three months after breast cancer surgery in the relationship between age and depressive symptoms. In women with moderate-to-severe pain, age was not associated with depressive symptoms but in women with mild or no pain, younger age was associated with greater depressive symptoms. However, in women with neuropathic pain, younger age was associated with greater

depressive symptoms, but not in women without neuropathic pain. The impact of pain was not age-related. High preoperative pain expectations may be a risk factor for pain three months after breast cancer surgery, regardless of age. In Chapter 5, results are integrated and discussed along with implications for future research and treatment.

DEDICATION

This dissertation is dedicated to the participants of these studies, who selflessly shared their time and experiences, despite their own suffering, so that cancer might hurt less for others.

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I am also grateful to my committee members, Dr. Alison Macpherson and Dr. Rebecca Pillai Riddell, for their guidance, support and mentorship during my time as a graduate student, and Dr. Jane Irvine, who played an important role in my early development as a researcher as well as my current development.

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CERTIFICATE OF AUTHENTICATION/AUTHOR CONTRIBUTIONS

Data from Chapters 2 and 3 are derived from a study originally designed by my PhD Dissertation supervisor, Dr. L. Gagliese. Data from Chapter 4 are derived from a larger, ongoing prospective study designed by Dr. Gagliese.

I coordinated the study from which Chapters 2 and 3 are derived, designed the research questions for the subanalyses in consultation with Dr. Gagliese, and developed the analysis plans. I collected the majority of the data and created and maintained the database. I benefitted from assistance with data collection from Ms. K.T.Tran, Ms. V. Treister, and Ms. L. Katz at various stages of the data collection process. Drs. R. Dworkin and R. Melzack provided the Short-Form McGill Pain Questionnaire-2. the measure which I validated in Chapter 2 and used in Chapter 3. I assisted with expanding the larger, ongoing prospective study, from which Chapter 4 is derived, to include one and two year follow-ups and collected the data (not included in this Dissertation). For Chapter 4, I designed the research question in consultation with Dr. Gagliese and developed the analysis plan. Data used in this chapter for this portion of the study were collected by Ms. A. Wood, Ms. N. Ciccone, Ms. V. Treister, Ms. C. Graham, Ms. K. Nunes, Ms. J. Jung, and myself.

For Chapters 2-4, I conducted the analysis and wrote the manuscripts. Dr. Gagliese provided invaluable guidance throughout each stage of the dissertation, including editorial input on all chapters. Importantly, she was readily available for discussion of issues related to carrying out the studies and interpretation of the findings.

Prior to submitting Chapter 2 for publication in PAIN, Dr. Dworkin provided feedback with respect to interpretation of the findings. Drs. Macpherson, Pillai Riddell, Dworkin, Melzack, Shepherd, Zimmermann, and Rodin read drafts of the manuscripts and provided editorial suggestions.

Signature: Lynn Gauthier Date: August 14, 2013

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CHAPTER 1

Age Differences in the Experience of Cancer Pain: A Literature Review

Dissertation Synopsis

Pain is one of the most common and feared symptoms of cancer (Cleeland, 1998). It increases in intensity as the disease progresses and significantly impairs quality of life (Bruera & Kim, 2003; Castel et al., 2007; Cleeland et al., 1994; M. Z. Cohen et al., 2005; Ferreira et al., 2008; McCarthy, Phillips, Zhong, Drews, & Lynn, 2000; Mystakidou et al., 2006; Peng, Wu, Sun, Chen, & Huang, 2006; Wells, Murphy, Wujcik, & Johnson, 2003). Although cancer can occur at any age, it is considered to be a disease of the older person (Canadian Cancer Society [CCS], 2013). With the aging population, the numbers of older people who will require treatment for cancer pain will grow. Unfortunately, our understanding of the experience of cancer pain across the adult life span is limited. We urgently need to improve our understanding in order to provide effective prevention and palliation of pain for adults of all ages.

The overall aim of this dissertation is to elucidate age-related patterns in the multidimensional experience of cancer pain.The introductory chapter presents an overview of the existing literature describing age-related patterns in cancer pain, and highlights methodological limitations and gaps in our knowledge. Evidence for the biopsychosocial model of pain is reviewed and methodological considerations in the study of age-related patterns in cancer pain are discussed. Chapter 2 presents an evaluation of the psychometric properties of the Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2 [Dworkin et al., 2009]), a revised and expanded version of the McGill Pain Questionnaire (Melzack, 1975), the most widely used measure of the multidimensional qualities of pain. This study represents the first evaluation of the psychometric properties

of the SF-MPQ-2 in people with cancer pain and the first evaluation of its invariance across age groups. This step was necessary prior to commencing the comprehensive investigation of age differences in the multidimensional experience of cancer pain and its correlates, which is presented in Chapter 3. In Chapter 3, it is also demonstrated that there are no age differences in depressive symptoms in people with cancer pain. This finding is consistent with studies of people with cancer pain (Green & Hart-Johnson, 2010; Kai-hoi Sze, Wong, Lo, & Woo, 2000; Knotkova, Clark, Mokrejs, Padour, & Kuhl, 2004; G. M. Williamson & Schulz, 1995), but not with other studies of people with cancer that do not consider pain (Compas et al., 1999; Kroenke et al., 2004; Politi, Enright, & Weihs, 2007; Schroevers, Ranchor, & Sanderman, 2004; Vinokur, Threatt, Vinokur-Kaplan, & Satariano, 1990; Wenzel et al., 1999). Cross-study methodological inconsistencies make it difficult to draw conclusions about the role of pain in the relationship between age and depressive symptoms in people with cancer. Chapter 4 therefore presents the first preliminary investigation of the moderating role of pain in the relationship between age and depressive symptoms in women who do and do not experience pain three months after surgery for breast cancer. In Chapter 5, the methodological and theoretical contributions of these findings are discussed as well as directions for future studies and implications for treatment.

Introduction

Cancer Pain

Although cancer can be accompanied by a constellation of disabling and distressing symptoms, pain is among the most common and feared symptoms (Cleeland,

1998). Over 80% of patients experience pain in the course of the disease (Bruera & Kim, 2003), with the prevalence and severity increasing as the disease progresses (Bruera & Kim, 2003; McCarthy, Phillips, Zhong, Drews, & Lynn, 2000; Peng, Wu, Sun, Chen, & Huang, 2006). Cancer pain is highly complex and heterogeneous (Bruera & Kim, 2003; Caraceni & Portenoy, 1999). It may be caused by tumor involvement or metastatic spread to soft tissue, viscera or bone (Bruera & Kim, 2003; Cleary & Carbone, 1997), or treatments, such as radiation, surgery or chemotherapy (Bruera & Kim, 2003; Caraceni & Portenoy, 1999; Jacox, Carr, & Payne, 1994; King & Arnold, 2005; McGuire, 2004). It may be nociceptive, arising from activation of afferent nerves in somatic tissue or viscera (Caraceni & Portenoy, 1999; Portenoy, 1989; Portenoy & Lesage, 1999) or neuropathic, arising from damage to the peripheral and/or central nervous systems (Backonja, 2003). A substantial number of patients may experience both types of pain (Grond et al., 1999). In fact, it has been estimated that 85% of patients experience more than one type of pain with 40% experiencing four or more types of pain (Twycross, Harcourt, & Bergl, 1996). Similar to nonmalignant pain, there is not a direct relationship between the extent of tissue damage and pain severity (Turk, 2002; Turk et al., 1998; Wu, Beaton, Smith, & Hagen, 2010). While the psychosocial correlates of nonmalignant pain have been well documented (Keefe, Rumble, Scipio, Giordano, & Perri, 2004), there has been significantly less attention to the role of these correlates in cancer pain. To date, the majority of the literature has focused almost exclusively on the biological correlates of cancer pain (Keefe, Abernethy, & Campbell, 2005; Turk, 2002). Nonetheless, there is emerging evidence that psychosocial factors are important in cancer pain (Keefe,

Abernethy, & Campbell, 2005; Turk et al., 1998), and the need for further research has been recognized (Turk & Fernandez, 1990).

Age-Related Patterns in Cancer Pain

Cancer is a disease of the older person (CCS, 2013). It has been estimated that 71% of new cases and 61% of cancer deaths occurred in people aged 60 and older (CCS, 2013). By 2031, 25% of Canadians will be aged 65 and older (Statistics Canada, 2007). Eighty percent of older cancer patients report pain (Walsh, Donnelly, & Rybicki, 2000), with more than half reporting severe pain (M. Z. Cohen, Musgrave, Munsell, Mendoza, & Gips, 2005). Unfortunately, older cancer patients may be less likely than younger patients to receive adequate pain treatment (Cleeland et al., 1994). There are significant gaps in our understanding of age-related patterns in cancer pain. They are outlined below in relation to key domains of interest, namely pain intensity, qualities, and interference.

Cancer Pain Intensity

Studies of age-related patterns in cancer pain intensity have been inconsistent. While some find that cancer pain increases with age (M. Z. Cohen et al., 2005; Yates et al., 2002), others find that it decreases (W. Y. Cheung, Le, Gagliese, & Zimmermann, 2011; Jordhoy et al., 2001; Mohile et al., 2011; Olden, Holloway, Ladwig, Quill, & van Wijngaarden, 2011; Soltow, Given, & Given, 2010; Stuver et al., 2012; Wilson et al., 2009), and still others find no relationship (Caraceni & Portenoy, 1999; Cataldo et al., 2013; Green & Hart-Johnson, 2010; Kelsen et al., 1995; McMillan, 1996; Rustoen, Fossa, Skarstein, & Moum, 2003; Valeberg, Miaskowski et al., 2008; Vigano, Bruera, & Suarez-Almazor, 1998; G. M. Williamson & Schulz, 1995). However, these studies suffer from a

number of methodological limitations which make it difficult to draw conclusions about the relationship between cancer pain and age. Many were not designed *a priori* to assess age-related patterns, thus older people are underrepresented (e.g. Caraceni & Portenoy, 1999; W. Y. Cheung et al., 2011; Jordhoy et al., 2001; Kelsen et al., 1995; Mohile et al., 2011; Olden et al., 2011; Stuver et al., 2012; Valeberg, Miaskowski et al., 2008; Wilson et al., 2009; Yates et al., 2002). Others used pain assessment tools that may not be valid for use across the adult life span (e.g. Kelsen et al., 1995; Olden et al., 2011; Soltow et al., 2010; G. M. Williamson & Schulz, 1995; Wilson et al., 2009; Vigano et al., 1998) . Additionally, many have confounded prevalence with intensity and do not report the number of people reporting pain by age group (e.g. Jordhoy et al., 2001; Mohile et al., 2011; Rustoen et al., 2003; Stuver et al., 2012; G. M. Williamson & Schulz, 1995; Wilson et al., 2009). This may be important, as one study found that although there may be age-related patterns in pain prevalence, among those who do report cancer pain, intensity is not age-related (Cataldo et al., 2013). However, a large systematic review found that the prevalence of cancer pain was not associated with age (van den Beuken-van Everdingen, M.H.J. et al., 2007). Unfortunately, these methodical limitations make it impossible to draw conclusions about age-related patterns, and they have hindered our understanding of cancer pain across the adult life span. Furthermore, these studies are limited in that they only tell us about pain intensity, or how much it hurts. Intensity alone insufficiently describes the multidimensional experience of pain (Jensen & Karoly, 2011). Consequently, extending the investigation of age-related patterns in cancer pain to other domains, including pain qualities, and pain-related interference in important life

domains, has substantial heuristic and clinical importance. This would provide us with a more refined understanding of age-related patterns in cancer pain and may contribute to tailored treatments. In Chapter 3, age related patterns in cancer pain intensity are described.

Cancer Pain Qualities

The qualities of pain, or "how it feels" (Jensen & Karoly, 2011), can provide information about its pathophysiology and guide the selection of appropriate treatments (Caraceni et al., 2004; Dworkin et al., 2007; Harden & Cohen, 2003; Mercadante, Casuccio, Pumo, & Fulfaro, 2000; Vadalouca et al., 2012). Unfortunately, there have been no studies designed specifically to investigate age-related patterns in cancer pain qualities. In studies that have simply reported on the relationship between age and scores on the McGill Pain Questionnaire (MPQ [Melzack, 1975]), younger age has been associated with higher scores in one study (Greenwald, 1991), while in another, age was not associated with MPQ Pain Rating Index scores (Wilkie, Huang, Reilly, & Cain, 2001). Our understanding of age-related patterns in cancer pain qualities remains seriously limited. In people with chronic nonmalignant pain, older people have obtained lower Total and Sensory scores on the MPQ or its short-form (Melzack, 1987) than younger people (Gagliese & Melzack, 1997a; Gagliese & Melzack, 2003). However, cancer pain may differ from chronic nonmalignant pain on a number of domains (Turk et al., 1998). It may therefore be inappropriate to generalize across patient populations. Studies assessing age-related patterns in the qualities of cancer pain are necessary. Chapter 2 reports on the first psychometric evaluation of the Short-Form McGill Pain

Questionnaire-2 (SF-MPQ-2 [Dworkin et al., 2009]), a revised and expanded version of the SF-MPQ, in older and younger people with cancer pain. The study described in Chapters 2 and 3 is the first study designed *a priori* to investigate age-related patterns in cancer pain qualities.

Cancer Pain Interference

More than one-third of cancer patients report that their pain interferes with psychological and physical functioning, including activities such as walking, working and socializing (Cleeland et al., 1994). Greater pain interference has been related to inadequate pain management, increased distress about pain and other symptoms, depression, anxiety, comorbidities and decreased functional status (Castel et al., 2007; Cleeland et al., 1994; Ferreira et al., 2008; Mystakidou et al., 2006; Vallerand, Templin, Hasenau, & Riley-Doucet, 2007; Wells, Murphy, Wujcik, & Johnson, 2003; G. M. Williamson & Schulz, 1995). Age-related patterns in cancer pain interference have received limited attention. In the small number of studies that have addressed this, age has been unrelated to pain interference (M. Z. Cohen et al., 2005; Green & Hart-Johnson, 2010; Soltow, Given, & Given, 2010; Wells, Murphy, Wujcik, & Johnson, 2003); however, in one study, older adults reported greater pain-related interference with walking than younger adults (Mohile et al., 2011). Unfortunately, these studies have not always taken into account a broad range of factors, including comorbidities and functional status, which may be important to consider when assessing age-related patterns. In Chapter 3, age related patterns in cancer pain interference are described.

Methodological Considerations

Several factors must be considered in the design and execution of studies of age-related patterns in cancer pain in order to maximize internal and external validity. First, the lack of a universal age-cutoff that defines older adults has limited cross-study comparisons (Gagliese, 2009). An age-group cutoff of 60 has been identified as having clinical relevance (Cataldo et al., 2013; Gagliese & Katz, 2003; Gagliese & Melzack, 2003; Gagliese, Weizblit, Ellis, & Chan, 2005; Green, Ndao-Brumblay, Nagrant, Baker, & Rothman, 2004; Green & Hart-Johnson, 2010; Kotkamp-Mothes, Slawinsky, Hindermann, & Strauss, 2005). For example, symptom clusters may differ between adults aged 60 and older and adults younger than 60 years old, adults aged 60 and older may also require longer time to achieve stable pain control than adults younger than 60 years old, and adults aged 60 and older may be less likely to be referred to psychosocial oncology than younger adults (W. Y. Cheung, Le, Gagliese, & Zimmermann, 2011; Ellis et al., 2009; Fainsinger et al., 2009). In this dissertation, adults aged 18 and over will be included and an age group cutoff of 60 years old for older adults will be used to maximize cross-study comparisons. Second, where possible, measures should be validated for use across the adult life span. Older and younger people should be equally able to use a tool and its validity and reliability should be similar across age groups (Gauthier & Gagliese, 2011). That way, if an age difference is detected, it may be interpreted as a possible age-related effect, rather than age differences in the way the tool operates. Chapter 2 describes age-related patterns in the use of the SF-MPQ-2. Third, missing data and loss-to-follow-up may be more likely with older than younger adults

due to declining health and functional limitations (Hardy, Allore, & Studenski, 2009). These issues may present threats to external validity (Garland, Carlson, Marr, & Simpson, 2009; Hardy, Allore, & Studenski, 2009; Mody et al., 2008; Ransom, Azzarello, & McMillan, 2006) and it has therefore been suggested that it may be necessary to over-sample older adults to obtain the required sample size in order to maximize power to detect an age-related effect (Gagliese, 2009).

Age-Related Patterns in the Correlates of Cancer Pain

In addition to assessing age differences in pain outcomes, such as pain intensity, qualities, and interference, it is important to consider whether their correlates vary with age. For example, in patients with chronic nonmalignant pain, there is emerging evidence suggesting that there are age-related patterns in the relationships between factors such as pain and depressive symptoms, regardless of age differences in those factors themselves (Cook, Brawer, & Vowles, 2006; Edwards, 2006; McIlvane, Schiaffino, & Paget, 2007; Turk, Okifuji, & Scharff, 1995). In one study, pain interference and life control mediated the relationship between pain intensity and depression in younger but not older patients (Turk, Okifuji, & Scharff, 1995). In a separate study, although younger and older people with chronic nonmalignant pain reported similar pain intensity and levels of activity, greater pain intensity was more strongly related to reduced functioning in younger than older people (Edwards, 2006). Taken together, these data suggest that even if there is no age difference in an outcome, there may be age-related variation in its correlates (Gagliese, 2009). Chapter 3 presents an analysis of age-related patterns in the correlates of cancer pain, including biomedical (e.g., disease and treatment factors, cancer symptom

severity, comorbidities, chronic nonmalignant pain, and functional status), psychological (e.g., quality of life, depressive symptoms, traumatic stress, spirituality, and pain-related acceptance, anxiety, attitudes, and catastrophizing) and social factors (e.g., marital status and satisfaction, social support, perceptions of significant others' responses to pain, and attachment style).

Although the correlates of chronic nonmalignant pain have been extensively studied across the biopsychosocial spectrum (Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Keefe, Rumble, Scipio, Giordano, & Perri, 2004), until recently, the biomedical model of cancer pain has predominated (Keefe, Abernethy, & Campbell, 2005; Turk, 2002). This lack of attention may reflect the historical understanding of cancer pain as somehow unique or distinct from other types of pain. However, this has been increasingly challenged in recent years, especially since, like most other types of pain, there is not an isomorphic relationship between the extent of tissue damage due to cancer and the intensity of pain (Turk et al., 1998; Wu, Beaton, Smith, & Hagen, 2010). Nonetheless, our understanding of the role of psychosocial factors in the experience of cancer pain is in its infancy (Porter & Keefe, 2011), especially in regards to older adults.

Life span developmental theory may contribute to our understanding of age-related patterns in correlates of cancer pain outcomes. This theory suggests that adults experience a series of gains and losses as they age, with the balance favouring gains in younger adulthood and shifting to losses in older adulthood (P. B. Baltes, 1987). It is possible that pain due to advanced cancer represents a life course disruption that is perceived as developmentally off-time among younger but not older adults (Gagliese et

al., 2009; Revenson & Pranikoff, 2005). Consistent with this, a recent qualitative study found age-related patterns in responses to living with cancer pain despite similar severity and interference across age groups (Gagliese et al., 2009). Older adults employed accommodative strategies, such as acceptance, whereas younger adults had difficulty accommodating to living with ongoing cancer pain. This was the first study to identify age-related patterns in adaptation to cancer pain, despite a lack of age differences in pain intensity and interference.

According to a life span developmental perspective, one's ability to adapt to lifecourse disruptions is also affected by a broad range of age-related biopsychosocial factors (Aldwin, Spiro, & Park, 2006). For instance, several unique physiological characteristics of older people, including greater comorbidity, polypharmacy, declining functional status, and the presence of nonmalignant chronic pain (Cancer and aging, 2007; Curless, French, Williams, & James, 1994; Davis & Srivastava, 2003; Extermann, 2000a; Mercadante, Casuccio, Pumo, & Fulfaro, 2000; Yancik & Ries, 2000) may contribute to pain homeostenosis, the decreased ability to effectively respond to the stress of ongoing pain (Karp, Shega, Morone, & Weiner, 2008) and may make older people more vulnerable to poor outcomes, such as prolonged recovery and impaired functioning (Gagliese, 2009). Thus, these issues must be considered in the examination of the impact of cancer pain across the adult life span, as their importance may change based on life stage, however to date, these issues have received limited attention.

The studies included in this dissertation draw on life span developmental theory (Aldwin, Spiro, & Park, 2006; Baltes, M. M.,& Carstensen, 1996; P. B. Baltes, 1987;

Schulz & Heckhausen, 1996) and the biopsychosocial model of pain (Gatchel, Peng, Peters, Fuchs, & Turk, 2007) as well as the cancer and nonmalignant pain research literature (Keefe, Rumble, Scipio, Giordano, & Perri, 2004; Keefe, Abernethy, & Campbell, 2005; Porter & Keefe, 2011; Turk et al., 1998) to identify the most salient factors to the experience of cancer pain across the adult life span. For most of these factors, prior research into age-related patterns in their relationship with cancer pain intensity, qualities, and interference, is not available. As such, the review of these factors below is limited by the available evidence. Each chapter also presents a more focused literature review relevant to the particular study.

Physical and Psychosocial Correlates

In addition to pain, cancer patients may experience multiple distressing symptoms, including fatigue, nausea, anorexia, shortness of breath, depression and anxiety (Bruera, Kuehn, Miller, Selmser, & Macmillan, 1991). Predictors of symptom distress and intensity include female sex, functional status and pain severity (Wilson et al., 2009; Zimmermann et al., 2010b). Symptom intensity may mediate the relationship between pain intensity and interference (Vallerand, Templin, Hasenau, & Riley-Doucet, 2007). While one study reported that age was not related to overall symptom intensity (Zimmermann et al., 2010b), another study reported that younger patients had a higher prevalence of distressing symptoms (Kirkova et al., 2010). These studies indicate that the severity of other cancer symptoms is important to consider, but it is difficult to draw conclusions about age-related patterns in the role of cancer symptoms because of the limited research and methodological differences across these studies.

Quality of life (QOL) can be broadly conceptualized as subjective wellbeing in the physical, social, and emotional domains (Felce & Perry, 1995; Hickey, Barker, McGee, & O'Boyle, 2005). Interestingly, when compared to younger people with chronic nonmalignant pain, older people report worse physical but better mental health QOL (Wittink et al., 2006). A similar pattern has been found in people with cancer; older patients report more physical but less psychological impairment than younger patients (Cimprich, Ronis, & Martinez-Ramos, 2002; Greimel, Padilla, & Grant, 1997; Jordhoy et al., 2001; Mohamedali et al., 2012; Schroevers, Ranchor, & Sanderman, 2004). In a recent study, older people with cancer pain had better emotional functioning but greater decline in physical functioning over time than younger people (Green & Hart-Johnson, 2010).

From 25 to 50% of patients with cancer pain report depressive symptoms (Hann, Winter, & Jacobsen, 1999; Lawrie, Lloyd-Williams, & Taylor, 2004; Lloyd-Williams, Dennis, & Taylor, 2004). Its prevalence and intensity increase as the disease progresses (Gibson, Lichtenthal, Berg, & Breitbart, 2006). Cancer patients with pain report greater depression than pain-free patients (Glover, Dibble, Dodd, & Miaskowski, 1995; Spiegel, Sands, & Koopman, 1994). Depression is related to greater cancer pain interference (Cleeland, 1984). Although there have been recent mixed findings (Linden, Vodermaier, MacKenzie, & Greig, 2012; Mystakidou et al., 2005; Nelson et al., 2009), it has been suggested that older adults are less affected by cancer than younger adults, and experience less depression, anxiety and distress (Blank & Bellizzi, 2008). In studies that do not measure pain, older cancer patients report lower depression than younger patients

(Compas et al., 1999; Kroenke et al., 2004; Politi, Enright, & Weihs, 2007; Schroevers, Ranchor, & Sanderman, 2004; Vinokur, Threatt, Vinokur-Kaplan, & Satariano, 1990; Wenzel et al., 1999). However, in the context of cancer pain, younger and older adults report comparable levels of depression (Gagliese, Gauthier, & Rodin, 2007; Green & Hart-Johnson, 2010; Kai-hoi Sze, Wong, Lo, & Woo, 2000; Knotkova, Clark, Mokrejs, Padour, & Kuhl, 2004; G. M. Williamson & Schulz, 1995). Cross-study differences in the operationalization of distress and depression (Nelson et al., 2009), or the measurement of distress and depression at different time points in the cancer continuum may contribute to the mixed findings. It may also be possible that certain symptoms, such as pain, operate as risk factors for depressive symptoms similarly across age groups, however, this has yet to be investigated.

Intrusive and avoidant thoughts indicative of clinically relevant traumatic stress may be common in cancer patients (Butler, Koopman, Classen, & Spiegel, 1999; Norton et al., 2004). Younger patients may report more intrusive thoughts and fewer avoidant thoughts than older patients (Butler, Koopman, Classen, & Spiegel, 1999; Hart et al., 2012; Schroevers, Ranchor, & Sanderman, 2004; J. Turner, Kelly, Swanson, Allison, & Wetzig, 2005) but these studies did not measure pain. Traumatic stress may be lower in older than younger adults with nonmalignant pain (Stalnacke & Ostman, 2010). However, the relevance of these findings in the context of cancer pain remains to be demonstrated.

Pain-related anxiety and catastrophizing may also be important to consider. In patients with nonmalignant pain, pain anxiety, or fearful and anxious reactions to pain-

related stimuli, is an important correlate of physical disability and psychological wellbeing (Burns, Mullen, Higdon, Wei, & Lansky, 2000; McCracken, Faber, & Janeck, 1998). Similar to younger adults (McCracken, Zayfert, & Gross, 1992), it has been related to worse self-rated health among older community dwelling adults (K. L. Bishop, Ferraro, & Borowiak, 2001). Older cancer and nonmalignant pain patients have reported lower pain anxiety than younger patients (Cook, Brawer, & Vowles, 2006; Mosher & Danoff-Burg, 2005).

Pain catastrophizing, which is characterized by rumination, magnification, and negative appraisals of one's ability to manage pain (Sullivan, Bishop, & Pivik, 1995), may also be used to convey distress and elicit support (Sullivan, Thorn, Haythorntwaite, Keefe, Martin, Bradley, & Lefebvre, 2001). Consistent with this, cancer patients who catastrophize report receiving more instrumental, but not emotional support from significant others (Keefe et al., 2003). However, in both nonmalignant and cancer pain patients, catastrophizing is related to greater pain interference and poorer functional wellbeing and QOL (S. Bishop & Warr, 2003; Boothby, Thorn, Overduin, & Ward, 2004; Novy et al., 2005; Sullivan, Thorn, Haythorntwaite, Keefe, Martin, Bradley, & Lefebvre, 2001). The evidence regarding age-related patterns in pain catastrophizing is mixed (Keefe & Williams, 1990; Sorkin, Rudy, Hanlon, Turk, & Stieg, 1990; J. A. Turner, Mancl, & Aaron, Jul 2004; Watkins, Shifren, Park, & Morrell, 1999). Interestingly, in one study, older patients with nonmalignant pain report greater catastrophizing than younger patients in the presence of mild but not severe pain (Watkins, Shifren, Park, & Morrell, 1999), therefore, pain severity may be an important mediator of these

relationships. Methodological differences, including different measures used to assess catastrophizing, may also account for the inconsistent findings across studies.

Pain acceptance involves acknowledging pain while redirecting efforts from attempts to control pain toward living a fulfilling life despite pain (McCracken, 1998). In patients with nonmalignant pain, it is related to better physical and psychological wellbeing (McCracken, 1998; McCracken & Eccleston, 2005; McCracken & Eccleston, 2006; Vowles, McCracken, & Eccleston, 2007; Vowles, McCracken, & Eccleston, 2008). We recently found that pain acceptance was an important correlate of psychological wellbeing, but not physical functioning in people with cancer pain (Gauthier et al., 2009). Similarly, in a recent qualitative study, acceptance emerged as a key method of positive adaptation to cancer pain (Gagliese et al., 2009). Specifically, older adults were more likely than younger adults to describe acceptance as a way to modify important activities and pursue goals despite cancer pain. In contrast, younger adults were more likely to describe being unable or unwilling to accept their pain. Quantitative studies of age-related patterns in acceptance of cancer pain are not available.

Spirituality is the meaning and value by which people understand and live their lives and it exists separately from religious belief systems (Brady, Peterman, Fitchett, Mo, & Cella, 1999; Muldoon & King, 1995). It has been related to both higher and lower nonmalignant pain intensity (Rosenstiel & Keefe, 1983; J. A. Turner & Clancy, 1986) but not pain interference (Abraido-Lanza, Vasquez, & Echeverria, 2004). While it is emerging as an important predictor of better physical and psychological wellbeing in patients with cancer (Brady, Peterman, Fitchett, Mo, & Cella, 1999; Canada, Murphy,

Fitchett, Peterman, & Schover, 2008; Lo et al., 2010), its role in adaptation to cancer pain is less understood. In older cancer pain patients, greater spirituality has been related to greater pain interference, but not intensity (M. Z. Cohen, Musgrave, Munsell, Mendoza, & Gips, 2005). Age-related patterns in spirituality and its relation to cancer pain remain to be elucidated.

Social support is an important predictor of wellbeing in cancer patients across age groups (Baider et al., 2003). In older patients, greater perceived support reduces feelings of uncertainty, anxiety and depression (Lien, Lin, Kuo, & Chen, 2009). Its relationship to cancer pain is less clear, with some studies finding it is related to lower pain and others finding no relationship (Kelsen et al., 1995; Koopman, Hermanson, Diamond, Angell, & Spiegel, 1998). While younger cancer patients have reported worse social functioning than older patients (Lintz et al., 2003), threatened social support has been associated with greater pain interference in both middle-aged and older adults (Peat, Thomas, Handy, & Croft, 2004). It is difficult to draw conclusions about age-related patterns in support and its impact on cancer pain because of the different definitions of support across studies (Zaza & Baine, 2002).

With specific regard to supportive responses to pain, perceptions of solicitous, distracting or negative or punishing responses to pain from significant others may be important correlates of cancer pain. In chronic nonmalignant pain patients, more frequently perceived solicitous responses predicts greater pain, pain-related disability and social support and more frequently perceived negative responses predicts lower pain and pain-related disability (Boothby, Thorn, Overduin, & Ward, 2004; Kerns,

Haythornthwaite, Southwick, & Giller, 1990; J. M. Romano, Turner, Jensen, & Friedman, 1995). However, a unique social context of cancer pain has been suggested whereby cancer patients are more likely than people with chronic nonmalignant pain to perceive more frequent solicitous responses from their significant others (Turk et al., 1998), therefore it may be inappropriate to generalize findings from people with chronic nonmalignant pain to people with cancer pain. Age-related patterns in perceptions of supportive responses to cancer pain have not been investigated.

The effectiveness of support depends on the extent to which one is able to elicit and respond to support (Mikulincer & Shaver, 2003). The attachment system is activated in response to perceived stressful situations, such as advanced disease (Mikulincer & Shaver, 2003; Rholes, Simpson, & Stevens, 1998). In studies of chronic nonmalignant pain, insecure attachment is associated with higher pain, depression and disability (Ciechanowski, Sullivan, Jensen, Romano, & Summers, 2003; Davies, Macfarlane, McBeth, Morriss, & Dickens, 2009; L. A. McWilliams, Cox, & Enns, 2000). In patients with advanced cancer, attachment anxiety buffered the effects of symptom distress on depressive symptoms and attachment security was associated with increasing age (Lo et al., 2009; Rodin et al., 2007). It is possible that age-related patterns in attachment security may impact on perceptions of support in relation to cancer pain; however, this has yet to be investigated.

Marital satisfaction is an important mediator of the relationships between pain and responses to pain. For example, negative responses are related to lower pain interference in non-maritally distressed patients only (Flor, Turk, & Rudy, 1989). Marital satisfaction

and collaborative coping may increase with advancing age (Dixon & Gould, 1996; Flor, Turk, & Rudy, 1989). For example, in a recent qualitative study, more older than younger patients described strengthened marital relationships arising from their partner's expressions of support and empathy. In contrast, more younger than older patients described marital strain and conflict related to their ongoing pain (Gagliese et al., 2009). These provocative results suggest age-related patterns in marital and relational functioning in the context of cancer pain, but large-scale, quantitative studies are needed.

BRIDGE FROM CHAPTER 1 TO CHAPTER 2

As described in Chapter 1, to date, the majority of studies of age-related patterns in cancer pain have focused on pain intensity (e.g. W. Y. Cheung, Le, Gagliese, & Zimmermann, 2011; Olden, Holloway, Ladwig, Quill, & van Wijngaarden, 2011; Stuver et al., 2012; Valeberg, Miaskowski et al., 2008). However, pain is multidimensional (Melzack & Casey, 1968) and intensity alone may not sufficiently describe its experience (Jensen & Karoly, 2011). Moreover, proper pain assessment is fundamentally important to pain management. The McGill Pain Questionnaire is the most widely used measure of the multidimensional qualities of pain. It has recently been expanded and revised but the validity and reliability of this revised tool, the Short-Form McGill Pain Questionnaire-2, in people with cancer pain and in people of different age groups has not been examined. This is necessary in order to ensure that the tool measures what it is supposed to measure the same way for older and younger people. In Chapter 2, the validity and reliability of this measure was investigated in older and younger people with cancer pain.

CHAPTER 2

Validation of the Short-Form McGill Pain Questionnaire 2 in Younger and Older People with Cancer Pain

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Introduction

Although cancer can occur at any age, it is a disease of older people (Canadian Cancer Society [CCS], 2013). Pain is among the most common symptoms (Cleeland, 1998), and increases in prevalence and severity as the disease progresses (Bruera & Kim, 2003; McCarthy, Phillips, Zhong, Drews, & Lynn, 2000; Peng, Wu, Sun, Chen, & Huang, 2006). With the aging of the population (Statistics Canada, 2007), there will be increasing numbers of older people who will require treatment for cancer pain. Unfortunately, it remains poorly understood and undertreated in older people (Bernabei et al., 1998; Cleeland et al., 1994; Gao, Gulliford, & Higginson, 2011; Higginson & Gao, 2012; Yun et al., 2004). Proper treatment requires assessment methodologies that are appropriate for use in people of all ages. However, some pain assessment scales have not been validated in older cancer patients. This is necessary to ensure that scales function similarly across age groups (G. W. Cheung & Rensvold, Apr 2002; G. W. Cheung & Lau, Apr 2012).

The McGill Pain Questionnaire (MPQ [Melzack, 1975]) and its short-form, the SF-MPQ (Melzack, 1987), are the most widely used measures of the sensory and affective qualities of pain (Jensen, 2003b). There is a strong body of evidence supporting their validity and reliability in people with cancer (Jensen, 2003b; Ngamkham et al., 2012). In people with chronic nonmalignant pain, the validity, reliability and feasibility of the MPQ and SF-MPQ are not age-related (Fuentes, Hart-Johnson, & Green, 2007; Gagliese & Melzack, 1997a; Gagliese & Katz, 2003; Gagliese & Melzack, 2003; Gagliese, Weizblit, Ellis, & Chan, 2005). Although older and younger adults report the

same pain intensity and choose the same words most frequently to describe their pain, older adults choose fewer sensory and affective words than younger adults (Gagliese & Melzack, 1997a; Gagliese & Melzack, 2003).

A revised version of the SF-MPQ, the SF-MPQ-2, has been published (Dworkin et al., 2009). It retains the sensory and affective qualities of the original SF-MPQ with additional neuropathic pain qualities. This is especially relevant to the assessment of cancer pain, which may be nociceptive (e.g. activation of afferent nerves in somatic tissue or viscera [Caraceni & Portenoy, 1999; Portenoy, 1989; Portenoy & Lesage, 1999]) or neuropathic (e.g. pain and sensory symptoms from damage to the peripheral and/or central nervous systems [Backonja, 2003]) or both (Grond et al., 1999). The 4-point intensity rating scale of the SF-MPQ was expanded to 11-point Numeric Rating Scales (NRS) to increase responsiveness (Dworkin et al., 2009). This response format is acceptable for use across the adult life span (Gauthier & Gagliese, 2011). The SF-MPQ-2 was validated initially in people with chronic pain and with diabetic neuropathy (Dworkin et al., 2009). Four subscales have been identified, including the original Affective subscale and three sensory subscales measuring Continuous, Intermittent and Neuropathic pain qualities. The SF-MPQ-2 has demonstrated good convergent validity with measures of pain and quality of life (QOL [Dworkin et al., 2009]). Its psychometric properties for assessment of cancer pain have yet to be investigated. Although the four-factor structure recently was confirmed in veterans with chronic nonmalignant pain (Lovejoy, Turk, & Morasco, 2012), the age range of the sample was restricted and analyses by age were not included. Thus, our understanding of the appropriateness of the

scale for older people remains limited. The objective of this study was to evaluate age-related patterns in the use of the SF-MPQ-2 and compare its psychometric properties in younger and older people with cancer pain. We hypothesized that, similar to people with chronic nonmalignant pain, (1a) older patients would choose fewer words than younger patients, but (1b) the most commonly chosen words would be selected by a similar proportion of older and younger patients and (1c) there would be no age related patterns in the intensity of each chosen word. (2) Construct and (3) convergent validity and (4) internal consistency reliability would not be age-related.

Methods

Participants

People attending outpatient clinics at a comprehensive cancer centre and those receiving home palliative care in Toronto, Canada, were recruited between May, 2006 and August, 2012 for a larger study of cancer pain (previously we have published separate analyses with smaller subsets of this sample that did not focus on the SF-MPQ-2 [Gauthier et al., 2009; Gauthier et al., 2012]). Patients who were ≥18 years of age, who had advanced cancer (metastatic or non-resectable disease [American Cancer Society, 2012a; National Cancer Institute, 2005]) and pain due to the disease or treatment, and sufficient English language ability to provide informed consent and complete the questionnaires were eligible for this study. Those with documented cognitive impairment as identified by their healthcare provider or medical chart, or those who scored below the cutoff score on our cognitive screen (Katzman et al., 1983), were not eligible to

participate. Ethical approval was obtained from the Research Ethics Boards of the University Health Network (UHN), York University and Mount Sinai Hospital.

Outpatients who reported pain to their healthcare providers were informed of the research study by clinic staff. Physicians providing home palliative care identified potentially eligible participants. The Research Assistant (RA) approached patients in the outpatient clinics or telephoned them if they were receiving home palliative care, then explained the study and obtained written informed consent from those who wished to participate. Following consent, the RA administered the Short Orientation Memory Concentration Test (SOMC [Katzman et al., 1983]). Those who scored <20 were withdrawn from the study. This cutoff has been shown to discriminate patients with and without cognitive impairment (Katzman et al., 1983) and has been used in studies of patients with similar disease characteristics (Rodin et al., 2007). The RA then collected demographic, disease and treatment-related information from eligible participants. They were provided with a questionnaire package which they completed with the help of the RA or took home to complete. Those who took the questionnaire home were provided with postage-paid, addressed envelopes and telephoned two weeks following recruitment if they had not returned the questionnaire package. Reasons for participant withdrawal were recorded.

Two age groups were formed, consisting of younger (aged 18-59) and older patients (aged $\geq$ 60 years old). These age groupings are consistent with previous studies of age differences in chronic nonmalignant, postoperative and cancer pain as well as psychological adjustment to cancer (Cataldo et al., 2013; Gagliese & Katz, 2003;

Gagliese & Melzack, 2003; Gagliese, Weizblit, Ellis, & Chan, 2005; Green, Ndao-Brumblay, Nagrant, Baker, & Rothman, 2004; Green & Hart-Johnson, 2010; Kotkamp-Mothes, Slawinsky, Hindermann, & Strauss, 2005). Initially, older patients were matched to younger patients based on sex and primary tumor type in a 1:1 matching system. When there were more older or younger patients in a given sex and primary tumor group (e.g. there were more older than younger men with genitourinary cancers; Figure 1), these additional patients were included in the analysis in order to maximize power to detect an age-related effect. This resulted in a sample of 244 patients (105 older and 139 younger patients) available for the analyses. Age groups were matched on these variables based on research suggesting possible sex and primary tumor type differences in cancer pain (Dobratz, 2008; Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009; Grond, Zech, Diefenbach, Radbruch, & Lehmann, 1996; Miaskowski, 2004; Vainio & Auvinen, 1996).

Twenty-five patients (5 older men and 4 older women; 7 younger men and 9 younger women) could not be matched because their cancer types did not match across gender and age. For instance, there was one older man with breast cancer but no younger men with breast cancer. These participants did not differ from the other 244 participants on demographic, disease or treatment factors (all $p \geq .08$). They were excluded from the analyses.

Measures

Pain Qualities. The Short-Form McGill Pain Questionnaire-2(SF-MPQ-2 [Dworkin et al., 2009]) was used to measure the qualities of pain. The initial version of the SF-MPQ-2

included items that assess 24 qualities of pain and the intensity of each quality on 11-point numeric rating scales (NRS). Participants were instructed to choose the number that best described the intensity of the pain and related symptoms they felt during the past week or to select zero if the word did not describe their pain or related symptoms. In the initial validation of the scale, the Total score was calculated from the mean of 22 items and scores for Continuous (throbbing pain, cramping pain, gnawing pain, aching pain, heavy pain, tender), Intermittent (shooting pain, stabbing pain, sharp pain, splitting pain, electric-shock pain, piercing), Neuropathic (hot-burning pain, cold-freezing pain, pain caused by light touch, itching, tingling or "pins and needles", numbness), and Affective (tiring-exhausting, sickening, fearful, punishing-cruel) subscales were calculated from the mean of the items included in each subscale. Two items, dull pain and squeezing-pressure, were not included in the final version of the SF-MPQ-2 because they did not differentiate people with and without neuropathic pain (Dworkin et al., 2009). We provide descriptive data for these items but do not include them in the psychometric analyses to remain consistent with the original validation study and subsequent studies validating the SF-MPQ-2 (Adelmanesh et al., 2012; Lovejoy, Turk, & Morasco, 2012).

Pain Intensity and Interference. The Brief Pain Inventory (BPI [Cleeland & Ryan, 1994]) was used to assess pain intensity and interference from pain. The BPI includes four items that assess Worst, Least and Average pain intensity in the last 24 hours and Current pain intensity on 11-point NRSs anchored with the words "no pain" and "pain as bad as you can imagine. The Average pain question was used as the measure of pain intensity. The BPI also includes seven 11-point NRSs, anchored with the words "does not interfere" and

"completely interferes", which assess interference from pain in general activity, mood, walking ability, work, relations with others, sleep and enjoyment of life. The Pain Interference score is calculated from the average of these seven items. The BPI has been used extensively in people with cancer pain and has good psychometric properties (Ger, Ho, Sun, Wang, & Cleeland, 1999; Radbruch et al., 1999).

Pain Relief and Analgesic Adequacy. Pain Relief was assessed with the BPI item that assesses relief from pain treatments or medications ranging from 0% (no relief) to 100% (complete relief). The adequacy of analgesia was assessed with the Pain Management Index (PMI [Cleeland et al., 1994]). This index is calculated by categorizing participants' scores on the BPI Worst Pain NRS into 4 categories (0: no pain; 1-3: mild; 4-7: moderate; 8-10: severe). This value is then subtracted from the score assigned to the highest level of analgesic prescribed (Breitbart et al., 1996; Cleeland et al., 1994) according to the World Health Organization's (WHO) Analgesic Ladder (World Health Organization, 1990).

Comorbidities. The Charlson Comorbidity Index (CCI [Charlson, Pompei, Ales, & MacKenzie, 1987]) was used to assess comorbidity load from 19 co-occurring conditions. The CCI is valid for use across the adult life span and with cancer patients (Extermann, 2000a). Higher scores indicate greater comorbidity. The RA completed the CCI by reviewing medical charts.

Functional Status. The Karnofsky Performance Status Scale (KPS [Karnofsky & Burchenal, 1949]) was used to assess functional status. It is an observer rated measure of patient functional autonomy and ability to participate in normal activities and self-care. Patient functional status is assessed on a scale ranging from 100 (normal activity, no

evidence of disease) to 0 (dead). Consistent with the typical methodology for completing the KPS (Abernethy, Shelby-James, Fazekas, Woods, & Currow, 2005; Mor, Laliberte, Morris, & Wiemann, 1984), it was completed by one rater through observation and by asking brief questions. It has good psychometric properties in people with cancer (Yates, Chalmer, & McKegney, 1980), including good interrater reliability (Yates, Chalmer, & McKegney, 1980; Zimmermann et al., 2010a). The KPS was completed by the RA at the time of recruitment.

Anticholinergic Load. The Anticholinergic Drug Scale (ADS [Carnahan, Lund, Perry, Culp, & Pollock, 2002; Carnahan, Lund, Perry, Pollock, & Culp, 2006]) was used to assess the cumulative anticholinergic load of all medications. The ADS assigns a score to medications based on their anticholinergic potency. A score is derived by summing the scores assigned to all medications prescribed and taken by patients. The ADS has been validated against serum anticholinergic activity in older people (Carnahan, Lund, Perry, Culp, & Pollock, 2002).

Depressive symptoms. The Center for Epidemiologic Studies – Depression Scale (CES-D [Radloff, 1977]) is a 20-item measure of current depressive symptoms and their frequency over the last week. It has been used extensively in people with cancer (Hann, Winter, & Jacobsen, 1999) and has excellent validity and reliability in people across the adult life span (Beeber, Shea, & McCorkle, 1998; Coyle & Roberge, 1992; Gauthier & Gagliese, 2011; Pasacreta, 1997).

Physical and Mental Health Quality of Life. The Medical Outcomes Study Short Form-36(SF-36 [Ware Jr. & Sherbourne, 1992]) Physical (PHC) and Mental (MHC) Health

Component Scores were used to assess physical and mental health quality of life (QOL). The SF-36 is the most commonly used measure of health-related QOL (Gauthier & Gagliese, 2011) and has been used in diverse patient populations with good reliability (Ware et al., 1995).

Data Analysis

Age differences in demographic, disease, and treatment characteristics were calculated with χ^2, Mann-Whitney U tests of medians and independent samples t-tests, where appropriate.

Items that were left blank were coded as missing. The count and percentage of missing data for each item on the SF-MPQ-2 was calculated. Age differences in the proportion of missing data on each item and the number of missing items were tested with χ^2 analyses and independent samples t- tests.

To test hypothesis (1a-c), the number of words chosen (responses $\geq$ 1/10) on the SF-MPQ-2, the proportion of patients choosing each item, the severity of each chosen item and the proportion of patients with moderate-to-severe ($\geq$5/10 on NRS) responses on each item were compared in older in younger patients using independent samples t-tests and χ^2 analyses. For this item analysis, a Bonferroni-corrected p value was used to control for multiple comparisons (adjusted $\alpha = .05/24 = .002$).

To test hypothesis (2), Confirmatory Factor Analysis (CFA) using Structural Equation Modeling (SEM) with Maximum Likelihood Estimation was used to test the construct validity of the SF-MPQ-2 according to the four subscales identified in previous validation studies (Dworkin et al., 2009; Lovejoy, Turk, & Morasco, 2012). Data were

first screened for outliers and violations of normality (Tabachnick & Fidell, 2012). Model fit was assessed with the standardized root mean square residual (SRMR < .08), root mean square of approximation (RMSEA < .10), comparative fit and Tucker-Lewis indices (CFI, TLI > .90) and the Akaike information criterion (AIC [Tabachnick & Fidell, 2012; Ullman, 2006]). Using multigroups analysis procedures (G. W. Cheung & Lau, 2012; Sass, 2011), the CFI difference test (ΔCFI) was evaluated to assess measurement invariance across age groups (G. W. Cheung & Rensvold, 2002). If $\Delta CFI \leq -0.01$, then the null hypothesis of invariance should be retained (G. W. Cheung & Rensvold, 2002). The ΔCFI test has been recommended over other Δ Goodness-of-fit Indices (GFI) as it is not dependent on model complexity or sample size and is less stringent than other ΔGFIs (G. W. Cheung & Rensvold, 2002). A baseline configural model was fit simultaneously for both age groups in order to test whether the factor structure was a reasonable fit and to compare to future, more constrained models. A measurement invariance model was then fit in order to determine whether the factor loadings were invariant across age groups. Finally, structural invariance was tested by constraining the correlations between the latent variables to determine whether the latent factor intercorrelations were similar across age groups (G. W. Cheung & Rensvold, 1999; Sass, 2011). Interscale correlations were then calculated separately for younger and older patients using Pearson's correlation coefficients. Fisher's Z-transformation was calculated to compare the significance of the difference of each interscale pairwise correlation between younger and older patients.

To test hypothesis (3), convergent validity was calculated using Pearson's correlation coefficients to assess associations between the Total and subscales of the SF-

MPQ-2 and measures of pain intensity (BPI Average Intensity), interference (BPI Interference), analgesic treatment factors (PMI, Relief from pain treatments), physical functioning (KPS, SF-36 PHC), depressive symptoms (CES-D) and mental health quality of life (SF-36 MHC). Analyses were conducted separately for younger and older patients and the magnitude of the correlations was compared with Fisher's Z-tests.

Finally, to test hypothesis (4), Cronbach's Alpha was calculated separately for younger and older patients. The internal consistency of the Total and subscale scores was then compared across age groups (Feldt, Woodruff, & Salih, 1987; Lautenschlager & Meade, 2008). All data were analyzed with SPSS or Analysis of Moment Structures (AMOS [Arbuckle, 1994]) version 20.

Results

Patient Characteristics

Five hundred and thirty-eight patients were approached between May 2006 and August 2012. Three hundred and ninety-seven (73.8%) patients consented to participate and 141 (26.2%) refused to participate. Reasons for refusal to participate were lack of interest (n=55, 39.0%), lack of time (n=30, 21.3%), illness/fatigue (n=20, 14.2%), lack of pain despite reporting pain to healthcare providers (n=18, 12.8%), patient reported language, comprehension or memory issues (n=6, 4.3%), and inability to answer emotional questions (n=1, 0.7%). Seven (5.0%) people did not provide a reason, and the family caregivers of four (2.8%) patients refused access to the patient. There were no sex differences between those who consented to participate and those who refused, but those

receiving home palliative care were more likely to refuse to participate (84.0%) than those who attended outpatient clinics (23.4%; $\chi^2(1) = 45.30, p \leq .0001$). The recruitment rate in home palliative care patients is consistent with previous studies (Husain et al., 2007) and reflects the severity of illness in this population. Eighty older people (80/538; 14.9%) refused to participate and 46 younger people (46/538; 8.6%) refused to participate. Age information was unavailable for 15 people (15/538; 2.8%) who refused to participate.

Of those who consented to participate, three participants (1.1%) ≥ 60 years old scored <20 on the SOMC and two participants (0.5%) < 60 years old reported that their pain was not cancer-related. These participants were withdrawn. One hundred and twenty-three people who initially consented to participate (123/397; 31.0%; 72 patients ≥ 60 years old, 51 patients < 60 years old) did not return the questionnaire package. Reasons for failing to return the questionnaire package were illness due to disease progression (n=44; 35.8%), death (n=38; 30.9%) and lack of interest in continuing to participate (n=17; 13.8%). Three participants (2.4%) said they returned their questionnaire package via mail however it did not arrive, and 21 participants (17.1%) did not return the questionnaire package for unknown reasons.

Compared to those who did not return the questionnaire package, those who returned the questionnaire package (n=269) were younger (57.56 ± 11.74 vs. 61.10 ± 13.55, p =.01), more likely to identify as Caucasian than non-Caucasian (73.9% vs. 56.4%, p =.001) and report that their primary language was English (72.1% vs. 55.9%, p =.01). Although gender was not associated with return of the questionnaire (p = .26),

more participants with breast (80% vs. 20%, p =.05) and gynecologic cancers (94.1% vs. 5.9%, p =.001) returned the questionnaire package and fewer participants with other cancers (e.g. unknown primary tumor, hematologic, skin, endocrine, central nervous system cancers; 46.2% vs. 53.8%, p =.001) returned the questionnaire package compared to those who did not. Those who returned the questionnaire package had higher KPS (79.33 ± 10.48 vs. 75.16 ± 12.75, p =.001) and SOMC scores (Mann-Whitney-U test of medians: 26 (IQR: 24, 28) vs. 26 (IQR: 24, 27.50), p =.001) than those who did not.

Demographic, disease and treatment characteristics of participants who matched on sex and primary tumor type and who were included in this analysis (n=244; see Participants) are presented in Table 1. The proportion of men and women in each age group did not differ. There were fewer older than younger single patients (11.4% vs. 20.9, p = .05), more older than younger widowed patients (15.2% vs. .7%, p = .001), more older than younger patients with elementary or high school as the highest level of education attained (45.7 vs. 29.5, p = .01), and fewer older than younger patients completing a college or bachelor's degree (38.1 vs. 51.1, p = .04).

There were more older than younger patients with genitourinary cancers (24.8% vs. 12.9%, p =.02), which is consistent with the incidence of some of these cancers in older adults (American Cancer Society, 2012b). There were no age differences in the duration of cancer or pain or the proportion of patients undergoing chemotherapy, radiation or hormone treatment. A similar proportion of older and younger patients reported concurrent chronic nonmalignant pain in addition to cancer pain. Although older and younger patients did not differ on anticholinergic load or polypharmacy, fewer older

than younger patients were prescribed an opioid (84.8% vs. 95.0%, $p = .007$). More older than younger patients had CCI scores >0 (49.5 vs. 24.5, $p = \leq .001$), and older patients had worse KPS functional status (76.00 ± 10.52 vs. 81.22 ± 10.25, $p \leq .001$) than younger patients.

Seven (2.9%; 5 [3.6%] younger and 2 [1.9%] older, $p = .69$) participants completed the questionnaire with the help of the RA. These participants reported better SF-36 MH QOL than those who did not complete the questionnaires with the RA (55.06 ± 10.86 vs. 43.11 ± 11.33, $p = .02$). There were no other differences between these two groups (all $p \geq .10$). The proportion of patients with missing SF-MPQ-2 data did not differ between those who completed the questionnaires with the RA and those who did not (28.6% vs. 22.1%, $p = .65$).

Detailed Analysis of the SF-MPQ-2

Missing data. In total, 54 participants (22.1%) had some missing data on the SF-MPQ-2. Of these, 36 (66.7%) had missing data on one or more items and selected ≥0/10 on the remaining items. Sixteen (29.6%) had missing data on one or more items and selected ≥1/10 on the remaining items. Only two participants (3.7%, 1 older and 1 younger) left all 24 items blank.

Participants with missing data were compared to those without missing data (n=190) on demographic, disease and treatment factors. Although those with missing data were older than those without missing data (60.57 ± 11.00 vs. 57.01 ± 11.55, $p = .04$), Cohen's d indicated this difference was small (Cohen's $d = .3$). There were no age group differences between those with complete versus missing data (Older: 26.7% vs. Younger:

18.7%, $p = .14$), or the median number of missing items (older: 2 vs. younger: 6, $p = .18$). An examination of the frequency of missing items revealed that the proportion of older and younger patients missing one item only versus ≥2 items did not differ (missing 1 item: 11.4% vs. 5.0%; missing ≥2 items: 15.2% vs. 13.7%, $p = .16$). There were no differences on other demographic, disease or treatment factors or study measures (all $p \geq .08$). Importantly, the older and younger patients did not differ on the highest level of education obtained (elementary or high school: 18.0% vs. college or bachelor's degree: 23.4% vs. postgraduate degree: 27.3%, $p = .4$) or SOMC scores (Mann-Whitney-U test of medians: 26 (IQR: 24, 28) vs. 26 (IQR: 24,28), $p = .7$).

Table 2 presents the proportion of missing data for each SF-MPQ-2 item for the total sample and for each age group. The amount of missing data for each item was low and ranged from 4.9% (Tiring-exhausting) to 9.8% (Piercing). There were no age differences in the proportion of those with missing data on each item.

Age differences in pain, depressive symptoms and QOL. Older and younger patients did not differ on BPI Average Pain Intensity (3.70 ± 2.12 vs. 4.00 ± 2.12, $p = .28$), Pain Interference (4.67 ± 2.48 vs. 4.93 ± 2.37, $p = .40$), PMI <0 (16.2% vs. 13.7%, $p = .58$), Relief from treatments or medications (66.28 ± 24.41 vs. 68.72 ± 24.54, $p = .51$), CES-D depressive symptoms (19.89 ± 11.06 vs. 21.60 ± 10.15, $p = .21$) or SF-36 physical (29.40 ± 7.86 vs. 29.03 ± 7.39, $p = .71$ or mental health QOL (44.28 ± 11.66 vs. 42.83 ± 10.54, $p = .31$).

Testing Hypothesis 1: Age-related patterns in the number and severity of words chosen.

Partially consistent with hypothesis (1a), that older patients would choose fewer words to describe their pain, older patients chose fewer Affective words than younger patients (1.77 ± 1.37 vs. 2.13 ± 1.28, $p = .04$). Cohen's d indicated this difference was small (Cohen's $d = -.3$). There were no age differences in the number of words chosen from the Continuous (older: 3.29 ± 1.87 vs. 3.51 ± 1.63, p=.34), Intermittent (older: 2.49 ± 2.05 vs. younger: 2.65 ± 1.97, $p = .52$) or Neuropathic subscales (older: 2.10 ± 1.62 vs. younger 2.39 ± 1.67, $p = .17$) or the overall number of words chosen (older: 10.60 ± 6.35 vs. younger: 11.62 ± 5.68, $p = .19$).

Consistent with hypothesis (1b), there were no age differences in the proportion of older and younger patients selecting each word (Figure 2; all $p \geq .02$). However, although their order differed, the same four words were selected by ≥2/3 of older and younger patients. Older patients selected aching pain (83.8%), tiring-exhausting (77.0%), sharp pain (72.0%) and dull pain (69.7%) most often, while younger patients selected tiring-exhausting (87.1%), aching pain, (79.2%), dull pain (76.3%) and sharp pain (67.7%) most often. Consistent with hypothesis (1c), there were no age differences in the severity of each word selected. Also, there were no age differences in the proportion of older and younger patients with NRS scores ≥ 5/10 on each item (Table 4).

Testing Hypothesis 2: Age-related patterns in construct validity. Four items were significantly skewed (splitting pain, electric-shock pain, cold-freezing pain and itching). A logarithmic transformation (ln+1) normalized the distributions and these transformed

items were included in the SEM. Using the 22-item scale, Confirmatory Factor Analysis tested the factor structure previously described (Dworkin et al., 2009; Lovejoy, Turk, & Morasco, 2012) in people with complete data (n=190).

Evaluation of the Mahalanobis distance revealed no multivariate outliers. A baseline configural model fit for both groups simultaneously demonstrated a reasonable fit, although the incremental fit indices, which may be sensitive to the magnitude of the correlations within the data (Kenny & McCoach, 2003), are just below the cutoff criteria (SRMR = .08, RMSEA = .07, CFI = .78, TLI = .75, AIC = 972.90). A fully constrained measurement invariance model was then fit (SRMR = .09, RMSEA = .07, CFI = .77, TLI = .74, AIC = 927.39). The ΔCFI test (ΔCFI = -0.01) indicated that this fully constrained measurement model was invariant across age groups, indicating that the overall fit of the model was the same for younger and older patients. In other words, consistent with hypothesis 2, younger and older patients associated the same SF-MPQ-2 items with the same latent factors or constructs (G. W. Cheung & Rensvold, 2002). The smaller AIC value in this model as compared to the baseline model suggests a better fit to the data (Ullman, 2006). Table 4 displays the standardized path coefficients for the final 22-items of the SF-MPQ-2 and the intercorrelations among the four latent factors for younger and older patients. Interestingly, itching had the lowest path coefficient for both younger and older patients. Finally, a structural invariance model was fit (SRMR = .10, RMSEA = .07, CFI = .76, TLI = .75, AIC = 970.44). The ΔCFI test (ΔCFI = -0.02) just failed to make the cutoff of $\leq$ -0.01 for invariance of the intercorrelations between the latent factors. Consistent with this, Fisher's Z-tests revealed that the strength of the correlation

between the Continuous and Intermittent and Continuous and Affective subscales was significantly stronger among older than younger patients (Table 5). There were no significant differences in the strength of the remaining interscale correlations.

A sensitivity analysis was conducted with data from the total sample (n=244), regardless of missing data. To retest the factor structure of the SF-MPQ-2 in younger and older patients regardless of missing data, full information maximum likelihood (FIML) model estimation was used to account for the missing data. The overall pattern of results was the same as with patients with complete data.

Testing hypothesis 3: Age-related patterns in convergent validity. Table 6 presents the tests of convergent validity among older and younger patients (n=244). The Total and subscales of the SF-MPQ-2 were correlated with more intense BPI Average pain. These correlations were positive and in the moderate-to-strong range suggesting that the SF-MPQ-2 and its subscales measure a dimension of pain that is closely related to pain intensity but sufficiently distinct to suggest that these may not be identical constructs. The SF-MPQ-2 was also associated with higher BPI Pain Interference and CES-D depressive symptoms, and lower Pain Relief and SF-36 Physical Health QOL and worse KPS functional status, further supporting the convergent validity of the SF-MPQ-2 in people with cancer pain.

Importantly, consistent with hypothesis 3, there were no age-related differences in the magnitude of most of the correlations when tested with a Fisher's Z-transformation. However, the correlations between the SF-MPQ-2 Continuous subscale and the SF-36 MHC, a measure of mental health QOL, were significantly stronger among older than

younger patients. Interestingly, there were moderate, significant correlations between the PMI and most of the subscales of the SF-MPQ-2 in younger, but not older patients and the correlation between the PMI and the SF-MPQ-2 Continuous subscale was significantly stronger in younger than older patients.

Testing Hypothesis 4: Age-related patterns in internal consistency reliability. Table 7 presents Cronbach's alpha for older and younger patients. It ranged from acceptable to excellent in each age group (Nunnally, 1978). In agreement with hypothesis 4, there were no age differences in the internal consistency reliability of the subscales of the SF-MPQ-2. Cronbach's alpha for the Total score was significantly greater for older than younger patients ($\chi^2(1) = 4.06, p = .04$).

Discussion

This study presents the first examination of the psychometric properties of the SF-MPQ-2 for the assessment of cancer pain, including the first comparison of its use and psychometric properties in older and younger people. We found no age differences in missing data, suggesting that older and younger people with cancer pain are equally able to complete the scale. They chose the same words to describe their pain with the same level of intensity, suggesting that there are no age differences in the way the scale is used or in the predominant qualities of cancer pain. We found evidence for good internal consistency reliability and convergent validity, which were similar across age groups. Consistent with previous reports (Dworkin et al., 2009; Lovejoy, Turk, & Morasco, 2012), a four-factor solution fit the data. Importantly, the same items loaded on each

factor across age groups, providing evidence for measurement invariance. Overall, the weight of the evidence suggests that the scale is appropriate for use in younger and older people with cancer pain.

The first consideration in determining the utility of an assessment tool is whether it can be completed by the group for whom it was designed (Streiner & Norman, 2008). Although it has been suggested that the MPQ is overwhelming for older people (Herr & Mobily, 1991; Herr & Garand, 2001), data supporting this claim are lacking. Instead, consistent with the majority of previous studies using the MPQ and SF-MPQ (Fuentes, Hart-Johnson, & Green, 2007; Gagliese & Melzack, 1997a; Gagliese & Katz, 2003; Gagliese & Melzack, 2003; Gagliese, Weizblit, Ellis, & Chan, 2005), we found no age-related patterns in the ability to complete the SF-MPQ-2. Most participants with missing data left three or fewer items blank. There were no age differences in the percentage of missing data overall or by individual item. Importantly, missing data was not associated with education, which is consistent with previous studies using the full MPQ (Cook et al., 2004; Gagliese, Weizblit, Ellis, & Chan, 2005; Wilkie et al., 2003). Given the available evidence, older and younger adults appear to be equally able to complete the SF-MPQ-2.

In studies of adults with chronic nonmalignant pain, while the most commonly chosen descriptors of pain are the same across age groups, older people choose fewer sensory and affective items than younger people (Gagliese & Melzack, 1997a; Gagliese & Melzack, 2003). Partially consistent with this, we found that older people chose fewer affective words to describe their pain. However, the effect size of this difference was small. Moreover, older people chose the same number of sensory qualities as younger

people. There are two possible explanations for these discrepant findings across patient populations: One involves the revised construction of the SF-MPQ-2, which may elicit a similar pattern of responding across age groups. Consistent with studies using the NRS, which have demonstrated a lack of age differences in pain intensity (Gagliese & Melzack, 1997a; Gagliese & Melzack, 2003; Gagliese, Weizblit, Ellis, & Chan, 2005; Green & Hart-Johnson, 2010; Valeberg, Miaskowski et al., 2008), we found no age differences in the intensity of each chosen quality. It is therefore possible that the use of NRSs on the SF-MPQ-2 may account for the present findings. A second possibility may be that the qualities of cancer pain override the previously documented parsimonious response style of older people with chronic nonmalignant pain. For example, because a substantial minority of cancer patients experience neuropathic pain (Bennett et al., 2012; Caraceni & Portenoy, 1999; Grond, Zech, Diefenbach, Radbruch, & Lehmann, 1996), the addition of neuropathic qualities to the SF-MPQ-2 may influence responding in a similar way across age groups. Future studies of age differences in the use of the SF-MPQ-2 in people with chronic nonmalignant or acute pain may clarify these discrepancies across patient groups.

In this sample of cancer patients reporting pain, we did not find support for the suggestion that older people are more reluctant to report pain (Yong, Bell, Workman, & Gibson, 2003) or less likely to endorse intense pain than younger people (Greenwald, 1991; Nicholas, Asghari, & Blyth, 2008; Oberle, Paul, Wry, & Grace, 1990). Instead, we found no age differences in the selection or intensity of each pain quality. These data are consistent with studies of people with chronic nonmalignant pain that have shown that older and younger people choose the same words most frequently to describe their

pain(Gagliese & Melzack, 2003). Taken together, there is little evidence to suggest that in clinical samples of patients seeking symptom management, older people are reluctant to report pain or endorse intense pain.

Construct validity, a critical component of psychometric evaluation, tests the extent to which a tool measures what it purports to measure (Jensen, 2003a) . Confirmatory factor analysis is one method of assessing construct validity (Jensen, 2003a). It tests how observed, measured variables converge on one or more unobserved, latent factors (Ullman, 2006). There is ongoing debate about the factor structure of earlier versions of the MPQ (Fernandez & Boyle, 2002; Holroyd et al., 1992; Holroyd et al., 1996; J. Katz & Melzack, 2011; Turk, Rudy, & Salovey, 1985; Wright, Asmundson, & McCreary, 2001), but the relevance of this to the SF-MPQ-2 is unclear. Our findings support the same four-factor solution — Continuous, Intermittent, Neuropathic, and Affective — that was previously found in diverse patient populations (Dworkin et al., 2009; Lovejoy, Turk, & Morasco, 2012) and extend it to the assessment of cancer pain.

Importantly, we found that the items that made up each latent factor were the same in older and younger patients with cancer pain. Related to this, the internal consistency reliability of the subscales, which estimates the degree to which a set of items are related to an underlying factor (Jensen, 2003a), did not differ across age groups. This is consistent with the evidence demonstrating a lack of age-related patterns in the factor structure of the MPQ (Fuentes, Hart-Johnson, & Green, 2007; Gagliese & Melzack, 1997a; Gagliese & Katz, 2003; Gagliese & Melzack, 2003; Gagliese, Weizblit, Ellis, & Chan, 2005). While the strength of the interscale correlations were in the moderate-to-

strong range for older and younger patients, the interscale correlations were somewhat stronger between the Continuous and Intermittent subscales and Continuous and Affective subscales in older than younger patients. The magnitude of the correlations in older patients was similar to those previously published (Lovejoy, Turk, & Morasco, 2012). Future, larger scale studies are required to further investigate the importance of these small age-related differences.

Convergent validity is an element of construct validity. It tests how well a scale correlates with other, known measures of the same construct (Jensen, 2003a). Consistent with the initial validation of the SF-MPQ-2 (Dworkin et al., 2009), tests of convergent validity revealed moderate-to-strong correlations with measures of pain intensity, pain interference, relief from pain medications or treatments, and functional status as well as small-to- moderate correlations with measures of physical health QOL and depressive symptoms. In further support of the convergent validity of the subscales, the correlations between the Affective subscale and the CES-D and SF-36 MHC were somewhat stronger than the correlations between the sensory subscales and these two measures of psychological functioning. There were no age-related patterns in the magnitude of most of these correlations. However, the SF-36 MHC was correlated with the sensory subscales of the SF-MPQ-2 in older, but not younger patients. Moreover, the correlation between the SF-MPQ-2 Continuous subscale and the SF-36 MHC was significantly stronger for older than younger patients. This may reflect age-related variation in the relationships between pain and some indices of emotional wellbeing (Cook, Brawer, & Vowles, 2006; Turk, Okifuji, & Scharff, 1995). For example, Turk et al.,(1995) found a

different relationship between pain and depression in older than younger patients with chronic nonmalignant pain. Interestingly, the PMI was correlated with most of the subscales of the SF-MPQ-2 in younger, but not older patients and the correlation between the PMI and the SF-MPQ-2 Continuous subscale was significantly stronger for younger than older patients. Although the PMI is the most widely used index of pain management adequacy (Deandrea, Montanari, Moja, & Apolone, 2008), its validity has been questioned (Russell, Aveyard, & Oxenham, 2006). Thus, the meaning of this finding remains unclear and requires further investigation. Since the majority of correlations were similar across age groups, we may conclude that the convergent validity of the SF-MPQ-2 is not age-related but that the relationship between pain and emotional wellbeing may be stronger in older than younger patients. This requires testing in future studies.

In summary, these preliminary data suggest that the SF-MPQ-2 is appropriate for use in older and younger people with cancer pain. However, several limitations must be considered in the interpretation of these findings. Patients completed the SF-MPQ-2 only once. Thus it was not possible to investigate age-related patterns in test-retest reliability of the SF-MPQ-2. It will be important for future studies to do this. The majority of participants in this study were receiving specialized symptom management at a comprehensive cancer center, therefore the generalizability of these data to patients not receiving such care remains to be tested. It will also be important to investigate the psychometric properties of this version of the scale in different patient populations, including those at different points in the disease trajectory, including the end of life.

In conclusion, these data demonstrate that the factor structure of the SF-MPQ-2 is equivalent across age groups and that older and younger patients who report cancer pain endorse the same words with the same intensity to describe their pain. Notably, they show that older people are not reluctant to endorse severe pain. There is emerging evidence of the sensitivity of the SF-MPQ-2 in people with chronic nonmalignant pain (Curtis, Osadchuk, & Katz, 2011). This should also be evaluated in people with cancer pain. Another important future direction would be to evaluate age-related patterns in the correlates of neuropathic and non-neuropathic sensory and affective pain qualities, separately. This would further our understanding of the predictive validity of the SF-MPQ-2 (Lovejoy, Turk, & Morasco, 2012), contribute to the identification of age- or life-stage-specific profiles of factors that are important to different pain qualities, and improve our understanding of cancer pain across the adult life span.

Table 1. Participant Characteristics

	Mean ± SD; N (%)			
	Total (n=244)	Younger (n=139)	Older (n=105)	$P \leq$
Age (years)	57.79 ± 11.51 (range: 21-87)	49.83 ± 7.19	68.34 ± 6.61	.0001
18-29	3 (1.2)			
30-39	9 (3.7)			
40-49	46 (18.9)			
50-59	81 (33.2)			
60-69	62 (25.4)			
70-79	34 (13.9)			
80-89	9 (3.7)			
Sex (Female)	142 (58.2)	87 (62.6)	55 (52.4)	.11
Ethnicity (Caucasian)	191 (78.3)	106 (76.3)	85 (81.0)	.38
Primary Language (English)	206 (84.8)	120 (87.0)	86 (81.9)	.28
Marital Status				
Single	41 (16.8)	29 (20.9)	12 (11.4)	.05
Married/Partnered	159 (65.2)	94 (67.6)	65 (61.9)	.35
Separated/Divorced	27 (11.1)	15 (10.8)	12 (11.4)	.88
Widowed	17 (7.0)	1 (.7)	16 (15.2)	<.001
Highest level of education completed				
Elementary or High School	89 (36.5)	41 (29.5)	48 (45.7)	.01
College or Bachelor's degree	111 (45.5)	71 (51.1)	40 (38.1)	.04
Postgraduate degree	44 (18.0)	27 (19.4)	17 (16.2)	.52
Primary Tumor Type				

Gastrointestinal	60 (24.6)	35 (25.5)	25 (23.8)	.81
Breast	47 (19.3)	31 (22.3)	16 (15.2)	.17
Lung	45 (18.4)	22 (15.8)	23 (21.9)	.23
Genitourinary	44 (18.0)	18 (12.9)	26 (24.8)	.02
Gynecological	32 (13.1)	23 (16.5)	9 (8.6)	.07
Head & Neck	16 (6.6)	10 (7.2)	6 (5.7)	.64
Site of recruitment				.41
Palliative care	189 (77.5)	112 (80.7)	77 (73.3)	
Pain	19 (7.8)	11 (7.9)	8 (7.6)	
Temmy Latner Centre	3 (1.2)	1 (.7)	2 (1.9)	
Other solid tumor clinics	33 (13.5)	15 (10.8)	18 (17.1)	
Cancer duration (median (IQR) months)	23.5 (11, 49.8)	24 (9, 48)	23 (11,50.5)	.63
Pain duration (median (IQR) months)	11 (4.5, 22)	12 (5, 24)	9.5 (4, 19)	.15
Concurrent chronic nonmalignant pain	66 (27.0)	34 (24.5)	32 (30.5)	.41
Prescribed an opioid	221 (90.6)	132 (95.0)	89 (84.8)	.007
ADS	2.47 ± 2.07	2.58 ± 2.24	2.32 ± 1.82	.35
Polypharmacy (count of medications taken)	6.89 ± 3.91	6.87 ± 4.00	6.91 ± 3.82	.93
Count of analgesics taken	2.54 ± 1.14	2.65 ± 1.21	2.39 ± 1.03	.09
Chemotherapy, radiation or hormone treatment	132 (54.1)	82 (59.0)	50 (47.6)	.08
Nonpharmacological pain treatment	142 (58.2)	81 (58.3)	61 (58.1)	.98
CCI >0	86 (35.2)	34 (24.5)	52 (49.5)	<.001
KPS	78.98 ± 10.67	81.22 ± 10.25	76.00 ± 10.52	<.001
SOMC (median [IQR])	26 (24, 28)	26 (24, 28)	26 (24, 28)	.24

Note. ADS, Anticholinergic Drug Scale; CCI, Charlson Comorbidity Index; KPS, Karnofsky Performance Status Scale; SOMC, Short Orientation Memory Concentration Test; IQR, Interquartile Range.

Table 2. SF-MPQ-2 missing data by item

	N (%) Missing			
	Total (n=244)	Younger (n=139)	Older (n=105)	$P \leq$
1. Throbbing pain	14 (5.7)	9 (6.5)	5 (4.8)	.57
2. Shooting pain	14 (5.7)	9 (6.5)	5 (4.8)	.57
3. Stabbing pain	16 (6.6)	9 (6.5)	8 (7.6)	.56
4. Sharp pain	14 (5.7)	9 (6.5)	5 (4.8)	.57
5. Cramping pain	14 (5.7)	9 (6.5)	5 (4.8)	.57
6. Gnawing pain	19 (7.8)	11 (7.9)	8 (7.6)	.93
7. Hot-burning pain	14 (5.7)	8 (5.8)	6 (5.7)	.99
8. Aching pain	15 (6.1)	9 (6.5)	6 (5.7)	.81
9. Heavy pain	21 (8.6)	13 (9.4)	8 (7.6)	.63
10. Tender	22 (9.0)	11 (7.9)	11 (10.5)	.49
11. Splitting pain	21 (8.6)	12 (8.6)	9 (8.6)	.99
12. Tiring-exhausting	12 (4.9)	7 (5.0)	5 (4.8)	.92
13. Sickening	16 (6.6)	9 (6.5)	7 (6.7)	.95
14. Fearful	19 (7.8)	9 (6.5)	10 (9.5)	.38
15. Punishing-cruel	19 (7.8)	10 (7.2)	9 (8.6)	.69
16. Dull pain*	14 (5.7)	8 (5.8)	6 (5.7)	.99
17. Electric-shock pain	21 (8.6)	12 (8.6)	9 (8.6)	.99
18. Squeezing-pressure*	21 (8.6)	11 (7.9)	10 (9.5)	.66
19. Cold-freezing pain	23 (9.4)	13 (9.4)	10 (9.5)	.96
20. Piercing	24 (9.8)	13 (9.4)	11 (10.5)	.77
21. Pain caused by light touch	18 (7.4)	10 (7.2)	8 (7.6)	.90
22. Itching	19 (7.8)	10 (7.2)	9 (8.6)	.69
23. Tingling or "pins and needles"	17 (7.0)	11 (7.9)	6 (5.7)	.50
24. Numbness	15 (6.1)	11 (7.9)	4 (3.8)	.19

*Excluded from the final scale by Dworkin et al., (2009)

Table 3. Item Analysis. Severity of individual SF-MPQ-2 items among those who chose each item (responses ≥1/10) and the proportion of patients with moderate-to-severe pain (responses ≥5/10)

	Severity of each item chosen					*N (%) with responses ≥5/10*		
	Younger		*Older*			*Younger*	*Older*	
	Mean ±SD	Range	Mean ±SD	Range	*P*	N (%)	N (%)	*P*
Throbbing pain	4.90 ± 2.35	1-10	5.13 ± 2.71	1-10	.62	44 (33.8)	26 (26.0)	.20
Shooting pain	5.37 ± 2.64	1-10	5.16 ± 2.48	1-10	.66	44 (33.8)	27 (27.0)	.27
Stabbing pain	5.84 ± 2.55	1-10	4.95 ± 2.45	1-10	.06	48 (36.6)	26 (26.8)	.12
Sharp pain	5.64 ± 2.66	1-10	5.13 ± 2.44	1-10	.21	57 (43.1)	41 (41.0)	.67
Cramping pain	5.31 ± 2.37	1-10	5.39 ± 2.43	1-10	.86	43 (33.1)	24 (24.0)	.13
Gnawing pain	5.23 ± 2.47	1-10	4.97 ± 2.36	1-10	.56	38 (29.7)	29 (29.9)	.97
Hot-burning pain	5.67 ± 2.71	1-10	5.42 ± 2.20	1-10	.64	35 (26.7)	21 (21.2)	.34
Aching pain	5.24 ± 2.49	1-10	5.16 ± 2.39	1-10	.83	61 (46.9)	45 (45.5)	.83
Heavy pain	5.67 ± 2.60	1-10	5.25 ± 2.63	1-10	.38	42 (33.3)	32 (33.0)	.96
Tender	5.07 ± 2.60	1-10	4.75 ± 2.39	1-10	.47	42 (32.8)	29 (30.9)	.76
Splitting pain	5.03 ± 2.54	1-10	4.72 ± 2.97	1-10	.65	21 (16.5)	17 (17.7)	.82
Tiring-exhausting	5.90 ± 2.67	1-10	5.93 ± 2.56	1-10	.93	77 (58.3)	53 (53.0)	.42

Sickening	4.29 ± 2.76	1-10	4.65 ± 2.77	1-10	.50	28 (21.5)	20 (21.1)	.82
Fearful	4.63 ± 2.95	1-10	5.24 ± 2.58	1-10	.32	29 (22.3)	20 (21.1)	.82
Punishing-cruel	5.76 ± 3.24	1-10	5.43 ± 2.62	1-10	.62[b]	30 (23.3)	19 (19.8)	.53
Dull pain [a]	4.39 ± 2.22	1-10	4.63 ± 2.30	1-10	.50	48 (36.6)	33 (33.3)	.60
Electric-shock pain	5.76 ± 2.81	1-10	4.63 ± 2.45	1-9	.14	30 (23.6)	12 (12.5)	.04
Squeezing pressure [a]	5.32 ± 2.63	1-10	5.49 ± 2.52	1-10	.76	39 (30.5)	25 (26.3)	.50
Cold-freezing pain	4.06 ± 2.38	1-8	5.25 ± 2.14	1-8	.15	6 (4.8)	11 (11.6)	.08
Piercing	5.48 ± 2.78	1-10	4.68 ± 2.20	1-10	.13[b]	32 (25.4)	20 (21.3)	.48
Pain caused by light touch	4.95 ± 2.59	1-10	4.27 ± 2.61	1-10	.17	37 (28.7)	19 (19.6)	.12
Itching	3.86 ± 2.53	1-10	3.81 ± 2.37	1-9	.94	15 (11.6)	10 (10.4)	.78
Tingling or "pins and needles"	4.96 ± 2.80	1-10	4.65 ± 2.48	1-10	.54	40 (31.2)	22 (22.2)	.13
Numbness	4.73 ± 2.67	1-10	4.96 ± 2.49	1-10	.64	42 (32.8)	27 (26.7)	.32

[a] Excluded from calculations of the Total and subscale scores by Dworkin et al

[b] Levine's test indicated unequal variances, p value for equal variances not assumed

Table 4. 22-item SF-MPQ-2 standardized path coefficients for younger and older patients (n=190).

	Continuous		Intermittent		Neuropathic		Affective	
	Younger	Older	Younger	Older	Younger	Older	Younger	Older
Throbbing pain	.61	.67						
Cramping pain	.50	.60						
Gnawing pain	.66	.67						
Aching pain	.65	.66						
Heavy pain	.72	.73						
Tender	.47	.52						
Shooting pain			.69	.78				
Stabbing pain			.63	.69				
Sharp pain			.69	.69				
Splitting pain*			.70	.75				
Electric-shock pain*			.55	.65				
Piercing			.68	.71				
Hot-burning pain					.65	.71		
Cold-freezing pain*					.57	.46		
Pain caused by light touch					.56	.58		
Itching*					.25	.25		
Tingling or "pins and needles"					.49	.54		
Numbness					.48	.46		
Tiring-exhausting							.73	.68
Sickening							.65	.65
Fearful							.63	.74

Punishing-cruel							.67	.78
Latent factor intercorrelations								
Continuous	1	1						
Intermittent	.66	.88	1	1				
Neuropathic	.74	.87	.63	.67	1	1		
Affective	.82	.86	.67	.83	.78	.76	1	1

* log transformed

Table 5. SF-MPQ-2 Interscale Correlations for Younger and Older Patients (n=190).

Younger	Intermittent	Neuropathic	Affective
Continuous	.50*[b]	.52*	.58*[a]
Intermittent		.47*	.51*
Neuropathic			.50*

Older	Intermittent	Neuropathic	Affective
Continuous	.74*[b]	.61*	.75*[a]
Intermittent		.62*	.69*
Neuropathic			.55*

* $P \leq .01$ two-tailed Pearson Correlation Coefficient

[a] $P \leq .05$ for Fisher's Z-test comparison of correlations between younger and older patients

[b] $P \leq .01$ for Fisher's Z-test comparison of correlations between younger and older patients

Table 6. Convergent validity for Younger and Older Patients.

	BPI Average Pain Intensity	BPI Pain Interference	PMI[c,d]	Pain Relief	KPS	SF-36 PHC	CES-D	SF-36 MHC
Younger								
Total	.67**	.63**	-.32**	-.34**	-.25**	-.23**	.27**	-.13
Continuous	.60**	.49**	-.32** [a]	-.21*	-.26**	-.19*	.19*	.01[b]
Intermittent	.55**	.54**	-.13	-.28**	-.25**	-.35**	.18*	-.07
Neuropathic	.53**	.51**	-.32**	-.34**	-.17*	-.20*	.34**	-.17
Affective	.57**	.62**	-.30**	-.31**	-.20*	-.18*	.42**	-.32**
Older								
Total	.55**	.56**	-.13	-.30**	-.29**	-.32**	.35**	-.36**
Continuous	.57**	.52**	-.07 [a]	-.28*	-.26**	-.29**	.25*	-.30** [b]
Intermittent	.45**	.44**	-.07	-.37**	-.27**	-.27**	.29**	-.26**
Neuropathic	.42**	.36**	-.12	-.18	-.14	-.25*	.30**	-.25**
Affective	.43**	.60**	-.04	-.24*	-.36**	-.30*	.38**	-.46**

* $P \leq .05$ two-tailed

** $P \leq .01$ two-tailed

[a] $P \leq .05$ for Fisher's Z-test comparison of correlations between younger and older patients

[b] $P \leq .01$ for Fisher's Z-test comparison of correlations between younger and older patients

[c] PMI <0 versus ≥ 0

[d] Spearman's rho

Note: BPI, Brief Pain Inventory; PMI, Pain Management Index; KPS, Karnofsky Performance Status Scale; SF-36 PHC, SF-36 Physical Health Component Score; CES-D, Center for Epidemiologic Studies Depression Scale; SF-36 MHC, SF-36 Mental Health Component Score

Table 7. Cronbach's alpha for SF-MPQ-2 Subscale and Total scores for Younger and Older Patients.

	Cronbach's Alpha
Younger n=113	
Total score	.89[a]
Continuous	.74
Intermittent	.84
Neuropathic	.69
Affective	.73
Older n=77	
Total score	.93[a]
Continuous	.83
Intermittent	.85
Neuropathic	.66
Affective	.81

[a] $P \leq .05$ for Cronbach's Alpha comparison between age groups

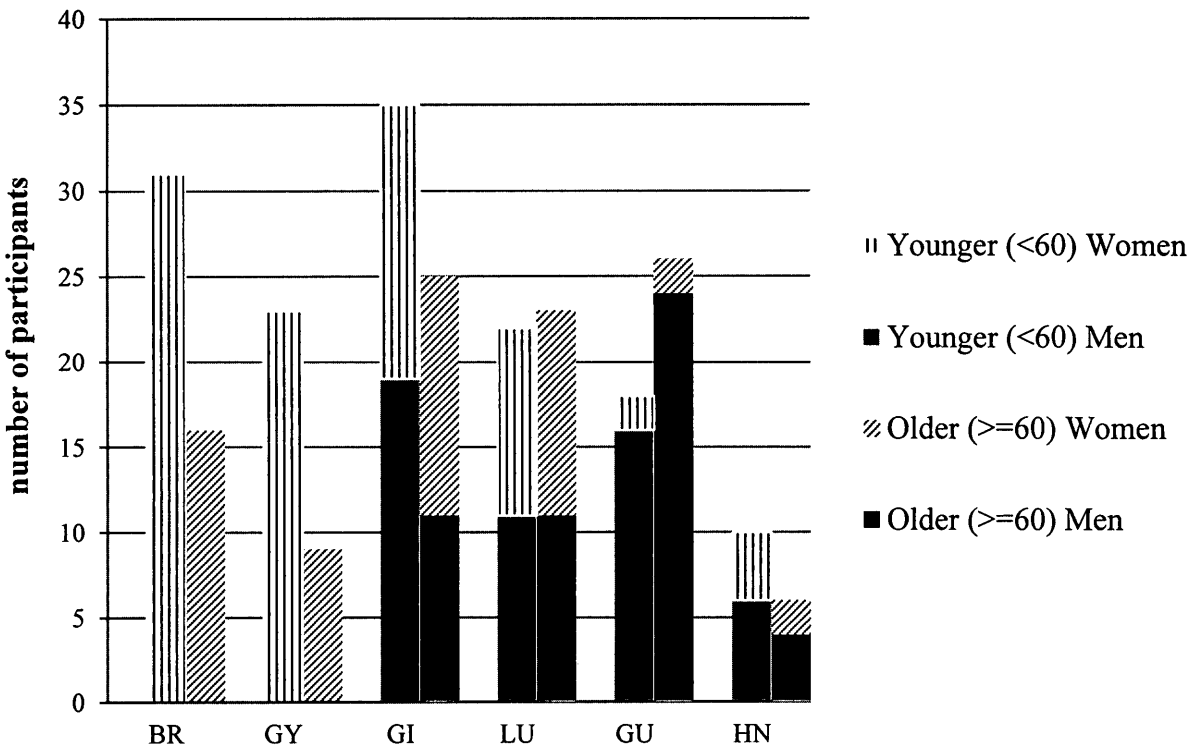

Figure 1. Number of participants in each sex/primary tumor group.

Note: BR, Breast; GY, Gynecologic; GI, Gastrointestinal; LU, Lung; GU, Genitourinary; HN, Head and Neck

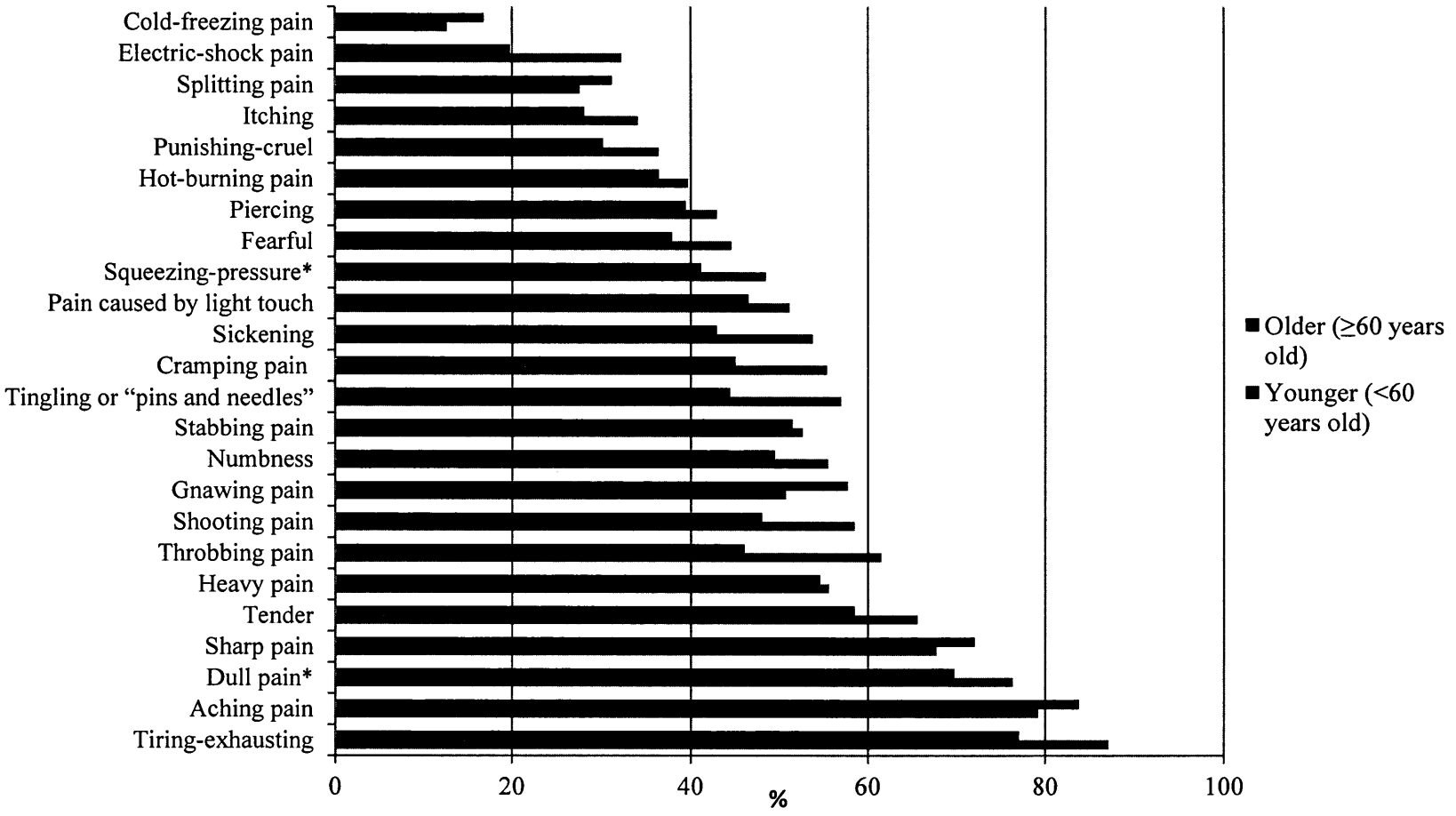

Figure 2. Proportion of Older and Younger patients selecting each SF-MPQ-2 item.

* Excluded from calculations of the Total and subscale scores by Dworkin et al. (2009)

BRIDGE FROM CHAPTER 2 TO CHAPTER 3

Existing studies of age-related patterns in cancer pain have primarily relied on the biomedical model (Keefe, Abernethy, & Campbell, 2005; Turk, 2002). However, there is not a direct relationship between the extent of injury and pain intensity (Turk et al., 1998; Wu, Beaton, Smith, & Hagen, 2010). There is also converging evidence that, consistent with chronic nonmalignant pain, biopsychosocial factors play a role in cancer pain (Keefe, Abernethy, & Campbell, 2005; Porter & Keefe, 2011; Turk, 2002). Moreover, studies of age-related patterns in cancer pain have mainly focused on pain intensity, a unidimensional construct. However, pain is multidimensional (Melzack & Casey, 1968) and therefore, investigations of age-related patterns in cancer pain should acknowledge this. In Chapter 2, we established that the Short-Form McGill Pain Questionnaire-2 is valid for use in older and younger adults with cancer pain. Now that we have established that the SF-MPQ-2 is appropriate for use in older and younger adults with cancer pain, in Chapter 3, we investigate age differences in the multidimensional experience of cancer pain using validated tools. Data described in Chapters 2 and 3 are derived from the same larger study of age-related patterns in cancer pain.

CHAPTER 3

Age-Related Patterns in the Multidimensional Experience of Cancer Pain

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Introduction

Pain is one of the most common and feared symptoms of cancer (Cleeland, 1998). It is associated with impairments in multiple domains of physical and psychosocial wellbeing (Castel et al., 2007; Cleeland et al., 1994; M. Z. Cohen, Musgrave, Munsell, Mendoza, & Gips, 2005; Ferreira et al., 2008; Keefe, Abernethy, & Campbell, 2005; Mystakidou et al., 2006; Turk et al., 1998; Wells, Murphy, Wujcik, & Johnson, 2003; G. M. Williamson & Schulz, 1995). Because the majority of new cases and deaths occur in people over the age of 60, cancer is considered a disease of older people (Canadian Cancer Society (CCS), 2013). While a number of age-related factors, including comorbidity, chronic nonmalignant pain, impaired functional status, and polypharmacy (Davis & Srivastava, 2003; Extermann, 2000a; Mercadante, Casuccio, Pumo, & Fulfaro, 2000; Yancik & Ries, 2000) may be associated with vulnerability to cancer pain, few studies have been designed to investigate age-related patterns in cancer pain or the impact of age-related factors. When age is considered, it is generally investigated as one of a number of other background demographic variables (Knudsen et al., 2009), rather than as the primary focus of the study. Consequently, our understanding of cancer pain across the adult life span remains limited. This information is urgently needed in order to provide effective palliation of pain to people across the adult life span.

Age-Related Patterns in Cancer Pain

There have been inconsistent findings of age-related patterns in the intensity of cancer pain, with reports of increases (M. Z. Cohen et al., 2005; Yates et al., 2002), decreases (W. Y. Cheung, Le, Gagliese, & Zimmermann, 2011; Jordhoy et al., 2001;

Mohile et al., 2011; Olden, Holloway, Ladwig, Quill, & van Wijngaarden, 2011; Soltow, Given, & Given, 2010; Stuver et al., 2012; Wilson et al., 2009) and no relationship with age (Caraceni & Portenoy, 1999; Cataldo et al., 2013; Green & Hart-Johnson, 2010; Kelsen et al., 1995; McMillan, 1996; Rustoen, Fossa, Skarstein, & Moum, 2003; Valeberg, Miaskowski et al., 2008; Vigano, Bruera, & Suarez-Almazor, 1998; G. M. Williamson & Schulz, 1995). Unfortunately, it is difficult to draw conclusions due to several methodological limitations. For instance, prevalence often has been confounded with intensity. Other methodological limitations include use of assessment tools that have not been validated for use in older people as well as the underrepresentation of older people. Moreover, much of the research has been limited to pain intensity (Caraceni & Portenoy, 1999; W. Y. Cheung, Le, Gagliese, & Zimmermann, 2011; Olden, Holloway, Ladwig, Quill, & van Wijngaarden, 2011; Stuver et al., 2012; Valeberg, Miaskowski et al., 2008). Extending our understanding of age-related patterns beyond this unidimensional construct is important, because intensity alone insufficiently describes the multidimensional nature of pain (Jensen & Karoly, 2011).

There has been substantially less investigation of age-related patterns in other dimensions of cancer pain, including the multidimensional qualities of pain and its interference in important daily activities and psychosocial wellbeing. There have been no studies designed specifically to investigate age-related patterns in cancer pain qualities. In studies that have simply examined age as one of a number of other background demographic variables and its relationship to scores on the McGill Pain Questionnaire (MPQ), the data are mixed. One study found that younger age was associated with higher

MPQ Sensory scores (Greenwald, 1991), while another found no age differences in MPQ Pain Rating Index scores (Wilkie, Huang, Reilly, & Cain, 2001). Most studies of pain interference find no age-related patterns (M. Z. Cohen et al., 2005; Green & Hart-Johnson, 2010; Soltow, Given, & Given, 2010; Wells, Murphy, Wujcik, & Johnson, 2003); however one study found that older adults reported greater pain-related interference with walking than younger adults (Mohile et al., 2011). Unfortunately, many of these studies suffer from the methodological weaknesses described above and have not taken into account a broad range of biopsychosocial, age-related factors. In studies of people with chronic nonmalignant pain that overcome these weaknesses, there were age-related patterns in pain qualities, but not intensity (Gagliese & Melzack, 1997a; Gagliese & Melzack, 2003). However, because cancer pain may differ from nonmalignant pain on a number of domains (Turk et al., 1998), it may be inappropriate to generalize across patient populations. Studies assessing age-related patterns in the multidimensional experience of cancer pain are therefore necessary.

Age-Related Patterns in Adaptation to Cancer Pain

Similar to people with chronic nonmalignant pain, in people with cancer, there is not a direct relationship between the degree of tissue damage and the intensity of pain experienced (Turk et al., 1998; Wu, Beaton, Smith, & Hagen, 2010). The biopsychosocial correlates of chronic nonmalignant pain have been well documented (Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Keefe, Rumble, Scipio, Giordano, & Perri, 2004). Although there is emerging evidence of their importance (Keefe, Abernethy, & Campbell, 2005; Porter & Keefe, 2011), the biomedical model of cancer pain has continued to dominate

(Keefe, Abernethy, & Campbell, 2005; Turk, 2002), limiting our understanding of the role of psychosocial factors in the experience of cancer pain.

The chronic nonmalignant pain literature may guide our understanding. For example, older people with chronic nonmalignant pain have reported worse physical health quality of life (QOL), but better mental health QOL than younger people (Wittink et al., 2006). While the evidence regarding pain catastrophizing is mixed (Keefe & Williams, 1990; Sorkin, Rudy, Hanlon, Turk, & Stieg, 1990; J. A. Turner, Mancl, & Aaron, Jul 2004; Watkins, Shifren, Park, & Morrell, 1999), older people with chronic nonmalignant pain have reported lower pain anxiety than younger people (Cook, Brawer, & Vowles, 2006; Mosher & Danoff-Burg, 2005). Cross-study methodological differences, including sample differences and different measures used to assess catastrophizing, may account for the mixed findings.

Studies of adaptation to cancer that do not consider pain may also have heuristic value. Interestingly, similar to people with chronic nonmalignant pain, older cancer patients report worse physical health QOL, but better mental health QOL, than younger cancer patients (Cimprich, Ronis, & Martinez-Ramos, 2002; Greimel, Padilla, & Grant, 1997; Mohamedali et al., 2012; Schroevers, Ranchor, & Sanderman, 2004). Older cancer patients have also reported lower traumatic stress and greater spirituality than younger patients (Baider et al., 2003; Lo et al., 2010; Schroevers, Ranchor, & Sanderman, 2004; Stalnacke & Ostman, 2010). Greater attachment security (Lo et al., 2009) and social support (Berg & Upchurch, 2007; Lintz et al., 2003) have been associated with older age, although the data are not always consistent, and relational quality may be an important

factor (Berg & Upchurch, 2007; Hunter, Davis, & Tunstall, 2006). Interestingly, although older cancer patients without pain may experience fewer depressive symptoms than younger patients (Compas et al., 1999; Kroenke et al., 2004; Politi, Enright, & Weihs, 2007; Schroevers, Ranchor, & Sanderman, 2004; Vinokur, Threatt, Vinokur-Kaplan, & Satariano, 1990; Wenzel et al., 1999), in the context of cancer pain, older and younger patients report comparable levels of depressive symptoms, suggesting that cancer pain may override the age differences found in depression when pain is not present (Gagliese, Gauthier, & Rodin, 2007). This illustrates the possible limitations of generalizing from other populations and the need to measure age-related patterns in people with cancer pain.

Age-Related Patterns in the Correlates of Cancer Pain

In addition to age differences in outcomes, it is also important to assess whether the pathways to those outcomes, or the correlates of those outcomes, vary with age (Gagliese, 2009). Specifically, there is an emerging literature that has demonstrated that despite a lack of age differences in factors such as pain intensity, pain interference, and depressive symptoms, there are age differences in the relationships between those factors in people with chronic nonmalignant pain (Cook, Brawer, & Vowles, 2006; Edwards, 2006; McIlvane, Schiaffino, & Paget, 2007; Turk, Okifuji, & Scharff, 1995). For example, although there were no age differences in pain intensity or activity, the relationship between pain intensity and functioning was stronger in older than younger people with chronic nonmalignant pain (Edwards, 2006). Similarly, in a recent qualitative study of people with advanced cancer and pain, age differences in pain intensity and

interference were not found, but there were age-related patterns in adaptation to cancer pain (Gagliese et al., 2009). On the one hand, older patients adapted by accepting pain and its associated limitations, pursued important life goals by modifying or pacing activities, and described strengthened relationships. On the other hand, younger patients described relational strain, and reacted to cancer pain with fear, anger, and grief at the loss of pre-pain identities and roles (Gagliese et al., 2009). Although a host of biopsychosocial factors have been associated with greater cancer pain intensity and interference, including female sex, longer disease duration, comorbidities, greater symptom severity, depression, pain catastrophizing, and worse physical functioning, quality of life, spirituality, and social support (Bernabei et al., 1998; S. Bishop & Warr, 2003; Caraceni & Portenoy, 1999; Castel et al., 2007; Cleeland et al., 1994; M. Z. Cohen et al., 2005; Ferreira et al., 2008; C. W. Given, Given, Azzouz, Kozachik, & Stommel, 2001; Green & Hart-Johnson, 2010; Kelsen et al., 1995; Mystakidou et al., 2006; Novy et al., 2005; Peat, Thomas, Handy, & Croft, 2004; Porter & Keefe, 2011; Soltow, Given, & Given, 2010; Stuver et al., 2012; Turk et al., 1998), age-related patterns in the interrelationships of many of these factors and their relationships to multidimensional pain outcomes, including pain intensity, qualities, and interference remain unknown.

By extending our investigation beyond pain intensity and adopting a biopsychosocial framework, we can obtain a richer understanding of the experience of cancer pain across the adult life span. Thus, our aims were to 1) examine age differences in the experience of cancer pain and 2) determine age-related patterns in the correlates of cancer pain intensity, qualities and interference. We hypothesized that (1a) there would

be no age differences in pain intensity or pain interference, but pain qualities would differ between older and younger patients; (1b) older patients would have more comorbidities and worse functional status, lower physical health QOL, traumatic stress, and pain anxiety, and higher mental health QOL, pain catastrophizing, pain acceptance, spirituality, social support and marital satisfaction than younger patients, but there would be no age differences in depressive symptoms; and (2) some of the correlates of pain outcomes would be similar across age groups, but unique correlates would also be evident within each age group. Specifically, in both age groups, female sex, comorbidities, functional status, symptom severity, depressive symptoms, pain anxiety, catastrophizing and social support would be related to pain outcomes. Pain acceptance and spirituality would be unique correlates of lower pain in older patients. Insecure attachment, less frequent solicitous and more frequent punishing responses, and lower marital satisfaction would be unique correlates of higher pain intensity, qualities and interference in younger patients. Since there is no evidence available to guide the development of hypotheses about outcome-specific profiles of correlates, we made no *a priori* hypotheses about this.

Methods

Participants

Data described in Chapter 2 and the present chapter are derived from the same study of age-related patterns in the experience of cancer pain. We have also previously examined different research questions using smaller subsets of these participants

(Gauthier et al., 2009; Gauthier et al., 2012). Patients attending outpatient clinics at a comprehensive cancer centre in Toronto, Canada and patients receiving home palliative care were recruited between May 2006 and August 2012. Inclusion criteria were age $\geq$ 18 years, advanced cancer, cancer-related pain, sufficient English to provide informed consent and complete questionnaires. Exclusion criteria included documented cognitive impairment as identified by healthcare provider or medical chart and scores below predetermined cutoff on a cognitive screening instrument (Katzman et al., 1983). Ethics approval for the study was obtained from the Research Ethics boards of the University Health Network, Mount Sinai Hospital and York University.

Healthcare providers of patients attending outpatient clinics and reporting pain determined their desire to be approached about the study by a Research Assistant (RA). Physicians providing home palliative care identified potentially eligible patients. The RA approached patients in person in the outpatient clinics or telephoned patients receiving home palliative care and explained the study. Patients agreeing to participate provided informed consent. The RA then administered the Short Orientation Memory Concentration Test (SOMC [Katzman et al., 1983]). Patients scoring <20 were withdrawn. The RA then collected demographic and clinical information from remaining participants. They were then provided with a questionnaire package which they could complete with the help of the RA or take home to complete. Those who chose to take the questionnaire package home were provided with a stamped, addressed envelope. Participants who had not returned their questionnaire were telephoned after two weeks with a reminder.

Measures

Demographic and clinical information. Demographic information collected included age, sex, ethnicity, marital status, and education. Clinical information included primary tumor type, cancer and pain duration, presence of chronic nonmalignant pain, and information regarding all modalities of treatment (pharmacologic and nonpharmacologic; see Chapter 2). The *Anticholinergic Drug Scale* (ADS [Carnahan, Lund, Perry, Culp, & Pollock, 2002; Carnahan, Lund, Perry, Pollock, & Culp, 2006]) was used to assess the cumulative anticholinergic load of all medications. A score is assigned to each medication based on its anticholinergic potency. Scores are summed to provide a total ADS score. The ADS has been validated against serum anticholinergic activity in older people (Carnahan, Lund, Perry, Culp, & Pollock, 2002).

Cognitive Screen. The Short Orientation-Memory-Concentration Test (SOMC [Katzman et al., 1983]) was used as a short cognitive screen. It is a 6-item screening measure of cognitive impairment and orientation to time, person and place, and memory. It has been validated for use among older adults (Katzman et al., 1983) and has been used in samples of patients with similar disease characteristics (Rodin et al., 2007).

Pain Measures. The Brief Pain Inventory (BPI [Cleeland & Ryan, 1994]) was used to measure pain intensity and its interference in 7 important life domains. It includes 11-point Numeric Rating Scales (NRS) anchored with the words "no pain" and "pain as bad as you can imagine" to assess Average, Worst, Least and Current Pain Intensity. The Average Pain Intensity question was used as our outcome measure of Pain Intensity because Current Pain may be unstable (Serlin, Mendoza, Nakamura, Edwards, &

Cleeland, 1995) and Worst Pain is not standardized for time across patients. BPI Average Pain Intensity has been used as an outcome measure (Langford et al., 2011; Valeberg, Miaskowski et al., 2008). The BPI also includes NRSs anchored with the words "does not interfere" and "completely interferes" to assess pain-related interference in general activity, mood, walking ability, work, relations with others, sleep and enjoyment of life. A Pain Interference score was calculated from the average of these questions. Internal consistency reliability in the present study was .91 in older patients and .91 in younger patients. The BPI has been validated in people with cancer pain (Ger, Ho, Sun, Wang, & Cleeland, 1999; Klepstad, Loge, Borchgrevink, Mendoza, & Cleeland, 2002). The BPI is also used to calculate the Pain Management Index (PMI [Cleeland et al., 1994]), an index of analgesic adequacy, based on the patient's report of worst pain and the highest level of analgesic prescribed, according to the World Health Organization's Analgesic Ladder (World Health Organization, 1986). Patients prescribed a strong opioid (e.g. morphine or fentanyl) were assigned a score of 3, patients prescribed a weak opioid (e.g. oxycodone) were assigned a score of 2, patients prescribed acetaminophen, acetylsalicylic acid, a nonsteroidal anti-inflammatory, or adjuvant drug (e.g. tricyclic antidepressant or gabapentin) were assigned a score of 1 and patients not prescribed any analgesic received a score of 0 (Breitbart et al., 1996; Cleeland et al., 1994). Patients reporting severe BPI Worst pain intensity (8-10) received a score of 3, patients reporting moderate BPI Worst pain (4-7) received a score of 2, patients reporting mild BPI Worst pain (1-3) received a score of 1 and patients reporting 0 on the BPI Worst pain item received a score of 0. BPI Worst pain category scores are subtracted from the Analgesic Ladder score to obtain a

score for the PMI. PMI scores <0 are considered inadequate analgesia (Cleeland et al., 1994). The *Short-Form McGill Pain Questionnaire 2* (SF-MPQ 2 [Dworkin et al., 2009]) was used to measure the qualities of pain. It includes 22 items that measure Continuous, Intermittent, Neuropathic and Affective pain qualities on 11-point NRSs. It has very good psychometric properties in patients with diverse pain conditions (Adelmanesh et al., 2012; Dworkin et al., 2009; Lovejoy, Turk, & Morasco, 2012). We have demonstrated that the SF-MPQ-2 has an equivalent factor structure in older and younger patients with cancer pain. See Chapter 2 for detailed analysis of the construct and convergent validity and internal consistency reliability in younger and older patients.

Physical Functioning Measures. The *Charlson Comorbidity Index* (CCI [Charlson, Pompei, Ales, & MacKenzie, 1987]) was used to measure comorbidities. The CCI predicts mortality based on the presence of 19 co-occurring conditions. It has been used extensively among cancer patients (Extermann, 2000a). Higher scores indicate greater comorbid load. The RA completed the CCI by reviewing medical charts. The *Karnofsky Performance Status Scale* (KPS [Karnofsky & Burchenal, 1949]) is an observer rated measure of functional status. The RA rated patient functional autonomy and ability to participate in their own care and regular activities on a scale ranging from 100 (normal activity, no evidence of disease) to 0 (dead) through observation and by asking brief questions at the time of recruitment. It has good psychometric properties in people with cancer (Yates, Chalmer, & McKegney, 1980), including good interrater reliability (Yates, Chalmer, & McKegney, 1980; Zimmermann et al., 2010a).

The *Edmonton Symptom Assessment Scale* (ESAS [Bruera, Kuehn, Miller, Selmser, & Macmillan, 1991]) measures the intensity of 9 cancer-related symptoms with 11-point NRSs. It has good validity and reliability in people with cancer (Bruera, Kuehn, Miller, Selmser, & Macmillan, 1991). The ESAS has demonstrated a 2 factor structure: One that includes physical symptoms (pain, tiredness, nausea, drowsiness, appetite, wellbeing, shortness of breath) and one that includes psychological symptoms (depression and anxiety) (W. Y. Cheung, Le, & Zimmermann, 2009). Since the psychological symptom cluster may have poor validity (Richardson & Jones, 2009; Teunissen, S. C. C. M, de Graeff, Voest, & de Haes, Jun 2007), we constructed an average score of the items assessing physical symptoms. We excluded the pain item in order to reduce the amount of shared variance between other measures of pain intensity and qualities. Internal consistency reliability in the present study was .77 in older patients and .80 in younger patients, and did not differ between the groups. The *Medical Outcomes Study Short Form-36* (SF-36 [Ware Jr. & Sherbourne, 1992]) *Physical Health Component Score* (PHC) measures subjective physical wellbeing in four domains, including physical functioning, role limitations caused by physical health, bodily pain, and general health perceptions. Scores are transformed to a 0 to 100 scale and higher scores reflect better physical health QOL. The SF-36 has demonstrated good psychometric properties in diverse samples of people (Ware et al., 1995). Internal consistency reliability in the present study was .68 and .69 in older and younger patients, and did not differ between the groups.

Psychological Wellbeing Measures. The *SF-36* (Ware Jr. & Sherbourne, 1992) *Mental Health Component Score* (MHC) measures subjective mental health and wellbeing in four domains, including mental health, vitality, social functioning, and role limitations caused by emotional health. Scores are transformed to a 0 to 100 scale and higher scores reflect better mental health QOL. Internal consistency reliability in the present study was .71 and .66 in older and younger patients, and did not differ between the groups. The *Center for Epidemiologic Studies – Depression Scale* (CES-D [Radloff, 1977]) was used to measure depressive symptoms. It is a 20-item measure of current depressive symptoms and their frequency over the last week. Scores range from 0 to 60 and higher scores reflect greater depressive symptoms. It has been used extensively and has excellent psychometric properties for use across the adult life span (Beeber, Shea, & McCorkle, 1998; Coyle & Roberge, 1992; Gauthier & Gagliese, 2011; Pasacreta, 1997). Internal consistency reliability in the present study was .89 and .88 in older and younger patients, and did not differ between the groups. The *Impact of Event Scale* (IES [Horowitz, Wilner, & Alvarez, 1979]) was used to measure symptoms of traumatic stress. It includes two factors that measure intrusive thoughts and avoidance of thoughts and ideas (Horowitz, Wilner, & Alvarez, 1979; Zilberg, Weiss, & Horowitz, 1982). It is the most common measure of traumatic stress symptoms in cancer patients (Gurevich, Devins, & Rodin, 2002). The total score ranges from 0 to 75 and higher scores reflect greater traumatic stress symptoms. It has good reliability among cancer patients with pain (Kaasa et al., 1993). Internal consistency reliability was .77 and .80 for the Avoidance subscale, .84 and .84 for the Intrusion subscale, and .88 and .90 for the Total, in older and

younger patients, and did not differ between the groups. The *Short Form Pain Anxiety Symptoms Scale* (PASS-20 [McCracken & Dhingra, 2002]) was used to measure anxiety reactions to pain-related stimuli. It includes four factors that measure fear of pain, physiological anxiety, escape and avoidant thoughts, and cognitive anxiety. The total score ranges from 0 to 100 and higher scores reflect greater pain-related anxiety. It has good validity and reliability in people with chronic nonmalignant pain (Roelofs et al., 2004). Internal consistency reliability was .84 and .77 for the Fear subscale, .73 and .76 for the Escape-Avoidance subscale, .80 and .77 for the Physiological Anxiety subscale, .86 and .87 for the Cognitive Anxiety subscale and .93 and .91 for the Total, in older and younger patients, and did not differ between the groups. The *Pain Catastrophizing Scale* (PCS [Sullivan, Bishop, & Pivik, 1995]) was used to measure excessive attention to pain-related thoughts and negative evaluations of painful sensations. Three factors have been identified that measure rumination about pain, a helplessness attitude toward managing pain, and exaggerated negative appraisals of painful sensations. The total score ranges from 0 to 52 and higher scores reflect greater pain catastrophizing. It has good psychometric properties in people with chronic nonmalignant pain and has been used to measure catastrophizing in people with cancer pain (S. Bishop & Warr, 2003; Buck & Morley, 2006). Internal consistency reliability was .90 and .89 for the Rumination subscale, .81 and .86 for the Magnification subscale, .90 and .88 for the Helplessness subscale, and .95 and .93 for the Total, in older and younger patients, and did not differ between the groups. The *Chronic Pain Acceptance Questionnaire* (CPAQ [McCracken, Vowles, & Eccleston, 2004]) measures the acceptance of pain. Two factors have been

identified that measure the activity engagement, or the degree to which people with pain participate in valued life activities despite pain, and pain willingness, or the willingness to experience pain without controlling it. The total score ranges from 0 to 120 and higher scores reflect greater acceptance of pain. Its validity has been demonstrated in people with chronic nonmalignant pain (McCracken, Vowles, & Eccleston, 2004). We have previously demonstrated that greater acceptance is associated with better psychological wellbeing in a smaller subset of this sample (Gauthier et al., 2009). Internal consistency reliability was .87 and .89 for the Activity Engagement subscale, .84 and .81 for the Pain Willingness subscale, and .85 and .89 for the Total, in older and younger patients, and did not differ between the groups. The *Pain Attitudes Questionnaire – Cancer* (PAQ-C [Tran et al., 2013; Yong, Gibson, Horne, & Helme, 2001; Yong, Bell, Workman, & Gibson, 2003]) was used to measure attitudes toward pain. In a smaller subset of this study, two factors were identified that measure pain-related Stoicism and Cautiousness to label sensations as painful (Tran et al., 2013). We have previously shown that Stoicism is related to greater CPAQ Activity Engagement, IES Avoidance and SF-MPQ-2 Neuropathic pain, and Cautiousness is associated with greater IES Avoidance and less satisfaction with pain control (Tran et al., 2013). The total scores for Stoicism and Cautiousness range from 1 - 5 and higher scores reflect greater pain-related stoicism and cautiousness. Internal consistency reliability was .87 and .90 for the Stoicism subscale, .88 and .84 for the Cautiousness subscale, in older and younger patients, and did not differ between the groups. *The Functional Assessment of Chronic Illness Therapy – Spiritual Wellbeing 12* (FACIT-Sp 12 [Peterman, Fitchett, Brady, Hernandez, & Cella,

2002]) was used to measure spirituality. It includes two factors that measure a sense of meaning, peace, and purpose in life; and comfort and strength derived from faith. The total score ranges from 0 to 48 and higher scores reflect greater spirituality. It has good validity and reliability with cancer patients (Peterman, Fitchett, Brady, Hernandez, & Cella, 2002). Internal consistency reliability was .91 and .87 for the Meaning-peace subscale, .87 and .88 for the Faith subscale, and .88 and .88 for the Total, in older and younger patients, and did not differ between the groups.

Social/Relational Measures. The *Medical Outcomes Study Social Support Survey* (MOS-SS [Sherbourne & Stewart, 1991]) measures perceptions of social support regardless of source. It includes four factors that measure perceptions of emotional, informational, tangible and affectionate support, and positive social interaction. It also queries the number of close friends and family; a measure of structural support. Scores are transformed to a 0 to 100 scale and higher scores reflect greater perceived support. It has good psychometric properties in patients with various chronic diseases (Sherbourne & Stewart, 1991). Internal consistency reliability was .91 and .90 for the Emotional Information subscale, .91 and .90 for the Tangible subscale, .90 and .88 for the Affectionate subscale, .89 and .89 for the Positive Social Interaction subscale, and .96 and .97 for the Total in older and younger patients, and did not differ between the groups. The *Multidimensional Pain Inventory (MPI) Caregiver Responses Scale* (Kerns, Turk, & Rudy, 1985) was used to measure patients' perceptions of their significant others' solicitous, distracting, and punishing responses to their pain. Scores for each subscale range from 0 to 6 and higher scores reflect more frequent perceptions of these responses.

The MPI has been validated with patients with chronic nonmalignant pain (Flor, Kerns, & Turk, 1987; Kerns, Turk, & Rudy, 1985; Kerns, Haythornthwaite, Southwick, & Giller, 1990). Internal consistency reliability was .80 and .81 for the Punishing responses subscale, .79 and .76 for the Solicitous responses subscale, and .73 and .72 for the Distracting responses subscale, in older and younger patients, and did not differ between the groups. The *Experiences in Close Relationships Inventory* (ECR [Brennan, Clark, & Shaver, 1998]) was used to measure adult attachment avoidance, the extent to which individuals are uncomfortable with closeness and dependence on others, and attachment anxiety, the extent to which individuals fear rejection and abandonment. Higher scores reflect greater attachment anxiety and avoidance. The ECR has good reliability in people with cancer and chronic nonmalignant pain (McWilliams & Asmundson, 2007; Rodin et al., 2007). Internal consistency reliability was .90 and .90 for the Avoidance subscale and .90 and .91 for the Anxiety subscale, in older and younger patients, and did not differ between the groups. The *Kansas Marital Satisfaction Scale* (KMS [Schumm, Paff-Bergen, & Hatch, 1986; Schumm et al., 1985]) was used to measure marital satisfaction. It is a three-item measure of satisfaction with the partner and relationship. Scores range from 3 to 21 and higher scores reflect greater satisfaction. It demonstrates good psychometric properties (Schumm, Paff-Bergen, & Hatch, 1986; Schumm et al., 1985). Internal consistency reliability was .98 and .98 in older and younger patients.

Data Analysis

Missing Data. SPSS Missing Value Analysis (MVA) was run to identify the number and percent of participants with missing data on each scale and the relationship

between missingness and other variables included in the study (Tabachnick & Fidell, 2012). The relationship between missing data on each scale and demographic (age, sex, ethnicity, primary language, marital status, education) and clinical factors (cancer type, cancer duration, pain duration, concurrent chronic nonmalignant pain, ADS, polypharmacy, treatment variables, CCI, KPS, WHO analgesic ladder level, PMI) was calculated with SPSS MVA. Little's Missing Completely at Random test (MCAR [Little, 1988]) is a likelihood ratio test of whether the data are missing completely at random (MCAR). It is a global test statistic that uses all available data to determine whether missing data on a given scale is associated with other variables in a dataset (Little, 1988). It overcomes the problems associated with multiple tests comparing the means of each variable between those with missing data and those without missing data (Little, 1988). A Bonferroni correction was applied to this analysis based on the number of tests of association between missingness on a given scale and the demographic and clinical variables and the remaining questionnaires (adjusted $\alpha = .05/64 = .0007$). Data were considered MCAR if missingness on a given scale was not associated with other variables that were measured in this study (Little, 1988). Data were considered Missing at Random (MAR) if missing data on a given scale was associated with other variables measured in this study. MCAR and MAR are considered ignorable conditions and allow for missing data estimation techniques to be employed (Heitjan & Basu, 1996). Data were considered Missing Not at Random (MNAR) if missing data was associated with itself (Resseguier, Giorgi, & Paoletti, 2011). For example, data would be MNAR if

participants with missing data on items about pain, such as pain catastrophizing and anxiety, had higher pain intensity than those without missing data on these items.

In order to identify age-related patterns in missingness, the count and percent of younger and older participants with missing data were calculated for each questionnaire. χ^2 analyses determined age differences in the proportion of younger and older participants with missing data. A Bonferroni correction was also applied to this analysis based on the number of tests of age differences in the proportion of patients with missing data on each scale (adjusted $\alpha = .05/48 = .001$).

For data that were MCAR and MAR, expectation maximization (EM) was used to impute missing data. EM is an iterative procedure that consists of two steps: In the first step, expected values are substituted for missing values based on the available data and current estimates of the parameters. In the second step, maximum likelihood, model parameters are re-estimated using the data from the first step (Tabachnick & Fidell, 2012). EM assumes a multivariate normal distribution of the data and that data is MCAR or MAR (Tabachnick & Fidell, 2012). Benefits of EM include lack of overfitting the data such that models converge better than they should, and less disturbance to variances than with other methods of imputation, such as mean substitution imputation (Tabachnick & Fidell, 2012). Data were not imputed for the MPI Caregiver Responses scale questions about the primary caregiver's identity and living arrangements, the structural support questions on the MOS (number of close family and friends variables) and KMS responses in unpartnered people that are completely missing. Missing PMI scores were calculated from the imputed value of the BPI Worst pain item. A comparison of analyses using the

imputed and nonimputed data revealed the same pattern of findings, therefore analyses from imputed data are presented.

Testing the study aims. Data were screened for assumptions of normality, linearity, and homogeneity of variance using grouped data screening procedures (Tabachnick & Fidell, 2012). To test age differences, independent-samples t-tests, Mann-Whitney U tests of medians and χ^2 analyses compared older and younger patients on demographic and clinical variables, and pain, physical and psychosocial factors. For the analysis, a Bonferroni-corrected p value was used to control for multiple comparisons (adjusted $\alpha = .05/44 = .001$).

A number of steps were taken to identify candidate correlates of BPI Average Pain Intensity, SF-MPQ-2 Continuous, Intermittent, Neuropathic and Affective subscales and BPI Interference. First, variables that differed between younger and older patients at $p \leq .05$ were retained for inclusion in each model. Second, candidate correlates that were associated with a given outcome variable in bivariate testing at $p \leq .01$, using the total sample (n=244), were considered for inclusion. Those that were highly associated with each other ($r \geq .6$ [Tabachnick & Fidell, 2012]) were examined for associations with the outcome variable. Where two or more highly correlated variables were identified, the variable that was more strongly related to the outcome variable was retained for entry into the model. These rigorous steps were taken in order to prevent multicollinearity and overfitting the models. Multivariate regression models, using backward elimination procedures, were fit separately for younger and older patients for each of the outcome variables, with the same candidate correlates in each age group. Criterion for removal of

variables was $p \geq .10$. The level of significance for correlates and model fit was set at $p \leq .05$. Model fit was evaluated, and VIF (≥ 10) and Tolerance ($\leq .10$) values were examined for evidence of multicollinearity (M. H. Katz, 1999; Tabachnick & Fidell, 2012). The strength of common correlates for a given outcome variable were compared between older and younger patients using the formula (Brame, Paternoster, Mazerolle, & Piquero, 1998; Clogg, Petkova, & Haritou, 1995; Field, 2009):

$$SE_{\text{b-difference}} = \sqrt{(SE_{bG1}^2 + SE_{bG2}^2)}$$

and

$$Z = \frac{b_{G1} - b_{G2}}{\sqrt{(SE_{bG1}^2 + SE_{bG2}^2)}}$$

where: $Z \geq (+/-)\ 1.645, \alpha = .05$
$Z \geq (+/-)\ 1.96, \alpha = .025$
$Z \geq (+/-)\ 2.33, \alpha = .01$
$Z \geq (+/-)\ 2.58, \alpha = .005$

In order to identify age differences in the moderating role of common and unique correlates identified in the multivariate regression models, simple interaction models were fit with the age group variable, the identified correlate and the relevant outcome variable. Continuous variables were grand-mean centered and product terms were created with the age group variable. Variables were entered in blocks, with age group, the centered correlate, then the two-way interaction between age group and the correlate (Aiken & West, 1991; Holmbeck, 2002). Significant interactions ($p \leq .05$) indicated that the correlate was significantly stronger for older or younger patients. Interactions were

investigated graphically by plotting the simple slopes of age group and the other variable(s) (Holmbeck, 2002). Only significant interactions are reported below.

Results

Participant Characteristics

Recruitment statistics for this study have been previously described (Chapter 2). Three hundred and ninety-seven (73.8%) patients who were approached about the study consented to participate. Three participants (1.1%) who consented were subsequently withdrawn because they did not meet the inclusion criteria. One hundred and twenty-three (31%) participants did not return the questionnaire package due to disease progression (35.8%), death (30.9%) and lack of interest in continuing to participate (13.8%). Two-hundred and sixty-nine participants returned the questionnaire package (Chapter 2).

As previously described (Chapter 2), two age groups were formed. Older ($\geq$60 years old) and younger (<60 years old) patients were matched based on sex and primary tumor type. This resulted in a sample consisting 105 older and 139 younger participants (total n=244). Twenty-five participants could not be matched based on sex and primary tumor type. As reported in Chapter 2, they did not differ from the matched sample (n=244) on demographic or clinical factors.

Demographic and clinical characteristics of the matched sample (n=244) have been previously described (Chapter 2). Briefly, older participants were 68.34 ± 6.61 years old and younger participants were 49.83 ± 7.19. Fewer older than younger patients were

single (11.4% vs. 20.9%, p =.05) and more older than younger patients were widowed (15.2% vs. .7%, p =.001) but there were no differences in the proportion of married/partnered (61.9% vs. 67.6%, p =.35) or separated/divorced (11.4 vs. 10.8%, p =.88) participants. Fewer older than younger patients had completed elementary or high school (45.7% vs. 29.5%, p =.01) or a post-secondary degree (38.1% vs. 51.1%, p =.04). There were minimal age differences in clinical characteristics. Older and younger patients did not differ on BMI (24.99 ± 5.72 vs. 24.74 ± 5.51, p = .73). There were more older than younger patients with genitourinary cancers (24.8% vs. 12.9%, p =.02), but the distribution of patients with other primary tumor types did not differ (breast: 15.2% vs. 22.3%; lung: 21.9% vs. 15.8%; gynecological: 8.6% vs. 16.5%; head and neck: 5.7% vs. 7.2%, all $p \geq .07$). Fewer older than younger patients were prescribed an opioid (87.0% vs. 95.6%, p =.03). There were no other age differences in demographic or clinical characteristics (see Chapter 2 for detailed description of demographic and clinical data by age group).

Missing Data

Overall, the percentage of patients with missing data on each scale was low. On most scales, <15% of patients had some missing data, except for the ECR Anxiety subscale (15.7%). Little's Missing Completely at Random test revealed that missing data on the KMS was associated with the MOS Tangible, Affectionate and Positive Social Interaction subscales (all $p \leq .0006$). Those with missing data on the KMS had lower Tangible (67.48 ± 29.84 vs. 83.07 ± 20.25), Affectionate 73.96 ± 30.00 vs. 89.19 ± 19.35) and Positive Social Interaction scores (70.77 ± 24.37 vs. 83.46 ± 20.03). Missing

data on the KMS can be considered Missing at Random because this pattern of missing responses may be explained by the marital status of those who did not complete the questionnaire. While it is possible that people who considered their marriages unsatisfactory left KMS items blank, it is also be possible that those who were partnered perceived greater social support than those who were not partnered. Data were MCAR for the rest of the scales (all $p \leq .01$).

Twenty-one percent of older patients and 7.7% of younger patients left one or more items blank (missing items) on the PASS-20 Cognitive Anxiety subscale ($p = .001$). However, there were no age differences in the proportion of patients who left all of the items blank on this subscale (3.5% vs. 3.2%, $p = .9$), and older and younger patients did not differ on the number of missing items within this subscale (1.71 ± 1.45 vs. 2.45 ± 2.02, $p = .24$). There were no other age differences in the proportion of patients with missing data on the rest of the questionnaires (all $p \geq .03$).

Data Screening

Grouped data screening procedures (Tabachnick & Fidell, 2012) revealed that KMS, MOS-SS subscales and MPI Punishing responses subscale were skewed for both age groups. A square root transformation normalized the MPI Punishing Responses distribution, but did not normalize the distributions of the MOS Total and subscales and the KMS. Various transformations were attempted with the MOS Total and subscales and the KMS, but they did not improve the distributions; therefore, the untransformed values were used for analyses. There were no other violations to assumptions of univariate and multivariate normality and homogeneity of variance in each age group. There were no

cubic or quadratic relationships between age (measured in years) and any of the variables. This was tested in order to ensure the appropriateness of the age groupings for the analysis.

Testing Aim 1. Age Differences in Physical Functioning, Psychosocial Wellbeing and Pain

The majority of patients (n=159; 65.2%) had CCI scores = 0. They ranged from 0-8 in older patients and 0-5 in younger patients. Since the CCI was positively skewed, it was collapsed to a dichotomous variable, representing no comorbidities (CCI = 0) and comorbidities (CCI > 0), to stabilize the distribution. Consistent with hypothesis (1b), older patients were more likely than younger patients to have CCI scores >0 (49.5% vs. 24.5%, $p \leq .001$). The most common comorbidities on the CCI were diabetes (n=30; 12.3%), chronic pulmonary disease (n=27; 11.1%), ulcer disease (n=13; 5.3%) and secondary solid tumor in the last 5 years (n=13; 5.3%). More older than younger patients had diabetes (18.1% vs. 7.9%, $p = .03$) and chronic pulmonary disease (20% vs. 4.3%, $p = .0003$) but there were no age differences in the proportion of people with ulcer disease (4.8% vs. 5.8%, $p = .99$) or secondary tumor (7.6% vs. 3.6%, $p = .27$).There were no age differences in the proportion of older and younger people reporting chronic nonmalignant pain of any type (30.5% of older patients vs. 24.5% of younger patients, $p = .41$; Chapter 2). Among older people, 50.0% attributed the pain to osteoarthritis, 9.4% to lower back pain, 3.1% to fibromyalgia and 37.5% to mixed causes. Among younger people, 32.4% attributed the pain to osteoarthritis, 23.5% to lower back pain, 8.8% to fibromyalgia and 35.3% to mixed causes.

There was further partial support for hypothesis (1b). Older patients had worse functional status than younger patients (KPS: 76.00 ± 10.52 vs. 81.22 ± 10.25, $p \leq .001$; Chapter 2). Older people also had lower IES Intrusion than younger people, but the proportion of older and younger people scoring >35 on the IES, a score that has been associated with possible post-traumatic stress (Thulesius, Alveblom, & Hakansson, 2004), did not differ (17% vs. 26%, $p = .10$). Also, there were no age differences in depressive symptoms (Table 1). 56% of older patients and 65% of younger patients scored ≥16 on the CES-D ($p = .14$), a cutoff that has been associated with clinically-relevant levels of depressive symptoms (Radloff, 1977). Inconsistent with the rest of the hypothesis, there were no age differences in SF-36 PHC and MHC, PASS-20, PCS, CPAQ, FACIT-Sp-12, MOS-SS and KMS. (Table 1; all $p \geq .03$).

Partially consistent with hypothesis (1a), there were no age differences in BPI Average Pain Intensity or Interference. A similar proportion of older and younger patients reported moderate-to-severe (≥5/10) BPI Worst (60.0% vs. 64.7%, $p = .45$) and Average (32.4% vs. 41.0%, $p = .17$) Pain Intensity and Pain Interference (48.6% vs. 46.8%, $p = .78$). However, inconsistent with this hypothesis, there were no age differences on SF-MPQ-2 Continuous, Intermittent, Neuropathic or Affective subscales (all $p \geq .11$).

Testing Aim 2. Age Differences in the Correlates of Pain Outcomes: Multivariate Linear Regression Models

Model building. All multivariate models included the variables that differed between older and younger patients at $p \leq .05$. These were marital status

(married/partnered, separated/divorced, widowed; single was reference category), education (post-secondary, post-graduate; elementary or high school was reference category), CCI > 0, KPS, receipt of an opioid, PASS-20 Cognitive Anxiety, IES Intrusion, and PAQ-C Cautiousness (Chapter 2 and Table 1, this Chapter). Table 2 lists additional candidate correlates of each outcome variable identified in bivariate testing.

Summary of final multivariate linear regression models. Table 3 presents a summary of the significant ($p \leq .05$) correlates across all final multivariate regression models. Partially consistent with hypothesis (2), functional status, symptom severity, and depressive symptoms were common correlates of pain outcomes. However, inconsistent with this hypothesis, pain willingness was a common correlate and gender and the social support measures did not emerge as correlates for older or younger patients. Also, comorbidity was important only for younger patients and there were age-related patterns in relationships between pain anxiety and catastrophizing and the pain outcomes. A detailed description of each final multivariate linear regression model follows below.

BPI Average Pain Intensity. Common correlates of higher BPI Average Pain Intensity in both older and younger patients were no concurrent chemotherapy, radiation or hormone therapy and higher ESAS Physical symptoms. There were no significant differences in the regression weights of the common correlates (all $p > .05$). Unique correlates of higher BPI Average Pain Intensity in older patients were education (post-graduate vs. elementary or high school) and lower KPS. Unique correlates of higher BPI Average pain intensity in younger patients were CCI >0, lower CPAQ Pain Willingness and higher IES Intrusion. An examination of the Tolerance and VIF values revealed no

multicollinearity. Both models were significant ($p \leq .001$) and accounted for 39.4% of the variance in older patients and 22.2% of the variance in younger patients (R^2 =.394 & .222; Table 4).

In the regression models, BPI Average Pain Intensity and PASS-20 Cognitive Anxiety were not significantly associated in older patients, but negatively associated in younger patients. A number of diagnostic steps were taken to determine why the direction of the association changed to negative only in the regression model for younger patients. First, an examination of Pearson's correlation coefficients separately in older and younger patients revealed PASS-20 Cognitive Anxiety and BPI Average Pain Intensity were correlated in older ($r = .27, p = .006$) but not younger patients ($r = .05, p = .56$). Second, the multivariate analysis was repeated using stepwise entry of PASS-20 Cognitive Anxiety, common correlates, and unique correlates. This analysis revealed that for younger patients, the direction of the relationship between BPI Average Pain Intensity and PASS-20 Cognitive Anxiety became negative when ESAS Physical symptom severity was entered into the model, suggesting a possible suppressor effect (J. Cohen & Cohen, 1983; MacKinnon, Krull, & Lockwood, 2000) in the model for younger patients.

SF-MPQ-2 Continuous Pain subscale. There were no common correlates of the SF-MPQ-2 Continuous pain subscale. In older patients, higher SF-MPQ-2 Continuous pain was associated with having chronic nonmalignant pain, no concurrent chemotherapy/radiation or hormone therapy and higher ESAS Physical symptoms. In younger patients, higher SF-MPQ-2 Continuous pain was associated with CCI >0, lower KPS and SF-36 PHC, and higher IES Intrusion. An examination of the Tolerance and

VIF values revealed no multicollinearity. Both models were significant ($p \leq .001$) and accounted for 29% of the variance in older patients and 24% of the variance in younger patients (R^2 =.293 & .242; Table 5).

There was a significant interaction between age and CCI on SF-MPQ-2 Continuous pain subscale scores (B = -1.365 (SE = .584), β = -.314, t = -2.337, p = .02). Post-hoc probing of simple slopes revealed that comorbidity was associated with greater SF-MPQ-2 Continuous pain subscale scores for younger, but not older patients (Figure 1).

SF-MPQ-2 Intermittent Pain subscale: There were also no common correlates of the SF-MPQ-2 Intermittent pain subscale. In older patients, higher SF-MPQ-2 Intermittent pain was associated with higher ESAS Physical symptoms and lower CPAQ Pain Willingness. In younger patients, higher SF-MPQ-2 Intermittent pain was associated with education (post-graduate degree vs. elementary or high school), CCI>0, lower SF-36 PHC and higher IES Intrusion. An examination of the Tolerance and VIF values revealed no multicollinearity. Both models were significant ($p \leq .001$) and accounted for 20.6% of the variance in older patients and 28.6% of the variance in the younger patients (R^2 =.206 & .286; Table 6).

Similar to the SF-MPQ-2 Continuous pain subscale findings above, there was a significant interaction between age and CCI on SF-MPQ-2 Intermittent pain subscale scores (B = -1.273 (SE = .626), β = -.229, t = -2.033, p = .04). Post-hoc probing of simple slopes revealed that comorbidity was associated with greater SF-MPQ-2 Intermittent pain subscale scores for younger, but not older patients (Figure 2).

SF-MPQ-2 Neuropathic Pain subscale. Common correlates of higher SF-MPQ-2 Neuropathic pain in both older and younger patients were lower SF-36 PHC and higher CES-D. There were no significant differences in the regression weights of the common correlates (all $p > .05$). There were no other significant correlates for older patients. Unique correlates for younger patients were longer disease duration, no opioid treatment and higher ESAS Physical symptoms. An examination of the Tolerance and VIF values revealed no multicollinearity. Both models were significant ($p \leq .0001$) and accounted for 16.5% of the variance in older patients and 33.7% of the variance in younger patients (R^2 =.165 & .337; Table 7).

SF-MPQ-2 Affective Pain subscale. Common correlates of higher SF-MPQ-2 Affective pain in both older and younger patients were higher ESAS Physical symptoms and IES Intrusion. There were no significant differences in the regression weights of the common correlates (all $p > .05$). In older patients, the only unique correlate was lower CPAQ Pain Willingness. In younger patients, unique correlates were lower KPS and higher PCS Total. An examination of the Tolerance and VIF values revealed no multicollinearity. Both models were significant ($p \leq .001$) and accounted for 43% of the variance in older patients and 36% of the variance in younger patients (R^2 =.433 & .363; Table 8).

BPI Pain Interference. Common correlates of higher BPI Interference in both older and younger patients included lower KPS and higher ESAS Physical symptoms. There were no significant differences in the regression weights of these correlates (all $p > .05$). Unique correlates in older patients included being prescribed an opioid and higher

PASS-20 Cognitive Anxiety. Unique correlates in younger patients included taking more analgesics, lower SF-36 PHC and higher IES Intrusion. An examination of the Tolerance and VIF values revealed no multicollinearity. Both models were significant ($p \leq .001$) and accounted for 49% of the variance in older patients and 44% of the variance in younger patients (R^2 =.493 & .440; Table 9).

In the regression models, BPI Interference was associated with lower PCS Total in older patients but higher PCS Total in younger patients. The regression weight was significantly different between older and younger patients ($SE_{b\text{-difference}} = .025$, $Z = 3.436$, $p \leq .005$). A number of diagnostic steps were taken to determine why the direction of the association was different between older and younger patients. First, an examination of Pearson's correlation coefficients between BPI Interference and PCS Total revealed that they were positively correlated in older ($r = .24, p = .01$) and younger patients ($r = .40, p = .001$). Second, the multivariate analysis was repeated using stepwise entry of PCS Total, followed by common correlates, then unique correlates. This analysis revealed that for older patients, the direction of the relationship changed once the common correlates, ESAS Physical symptoms and KPS, were entered into the model.

In order to explore the impact of ESAS Physical symptoms and KPS on the relationship between PCS Total and BPI Interference in older and younger patients, Structural Equation Modelling using multigroups analysis procedures (G. W. Cheung & Lau, 2012; Sass, 2011) was used. This analytic technique was used in order to model KPS and ESAS Physical symptoms in the same model, rather than fitting 2 separate models for each mediator (Frazier, Tix, & Baron, 2004). Model fit was evaluated with the

root mean square of approximation (RMSEA < .10), comparative fit and Tucker-Lewis indices (CFI, TLI > .90 [Tabachnick & Fidell, 2012; Ullman, 2006]). In the first step, invariance across age groups was assumed by fitting a fully constrained model. This model was an excellent fit to the data (RMSEA = .000; CFI = 1.000; TLI = 1.007). In the second step, coefficients for paths a1-2, b1-2 and c (Figure 3) were allowed to vary. This model was also an excellent fit to the data with minor deterioration of fit (RMSEA = .062; CFI = .994; TLI = .933). The results of this model were similar to the results of the regression models. PCS Total and BPI Interference were positively associated in younger patients, but negatively associated in older patients, suggesting a possible suppressor effect of ESAS Physical symptoms and KPS on the relationship between PCS Total and BPI Interference for older but not younger patients.

The CFI difference test ($\Delta CFI \leq .001$ [G. W. Cheung & Rensvold, 2002]) was used to compare the constrained and unconstrained models. ΔCFI was below the cutoff for retaining the null hypothesis of invariance (G. W. Cheung & Rensvold, 2002), therefore the fit of the model did not differ for older and younger patients. Further exploration of indirect effects using bootstrapping (500 random samples) and the bias-corrected confidence interval (CI: 95% [G. W. Cheung & Lau, 2008; MacKinnon, Lockwood, & Williams, 2004; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002]) revealed that ESAS Physical symptoms significantly mediated the relationship between PCS Total and BPI Interference for older ($B_{indirect}$ = .036, Standard Error (SE) = .011, 95% CI = .017-.063, p = .003) and younger patients ($B_{indirect}$ = .025, Standard Error (SE) = .008, 95% CI = .012-.048, p = .001). Examination of the indirect effects for KPS

revealed that it also mediated the relationship for older patients ($B_{indirect}$ = .014, Standard Error (SE) = .009, 95% CI = .002-.079, p = .004). The indirect effect for younger patients was just significant ($B_{indirect}$ = .008, Standard Error (SE) = .006, 95% CI = .000-.024, p = .051), suggesting that the impact of KPS on the relationship between PCS and BPI Interference was somewhat stronger among older than younger people.

Discussion

This study improves our understanding of the experience of cancer pain across the adult life span by investigating a broad range of biopsychosocial correlates of the multidimensional experience of cancer pain and elucidating how these factors operate together in relation to cancer pain in older and younger patients. There were no age differences in the intensity of cancer pain or its interference in important aspects of daily living, but older patients were less likely than younger patients to be prescribed an opioid. Despite the lack of age differences in pain outcomes, consistent with emerging literature demonstrating age differences in the correlates of chronic nonmalignant pain (Cook, Brawer, & Vowles, 2006; Edwards, 2006; McIlvane, Schiaffino, & Paget, 2007; Turk, Okifuji, & Scharff, 1995), we identified unique age-related patterns in the correlates of cancer pain. Specifically, this is the first study to identify comorbidities as a risk factor for pain outcomes in younger but not older patients and chronic nonmalignant pain as a risk factor in older but not younger patients. It is also the first study to identify possible unique roles of cancer symptoms and functional status in the relationship between pain catastrophizing and interference among older but not younger patients. These findings suggest that age-tailored multimodal assessments and treatments for cancer pain may be

necessary and they may inform the development of interventions that consider the unique needs of adults at different life stages.

There were no age differences in pain intensity, qualities or interference from pain. Despite this, although not statistically significant based on a stringent alpha level adjusted for multiple comparisons, older patients were somewhat less likely to be prescribed an opioid than younger patients. Unfortunately, this trend is consistent with data from two decades ago (Cleeland et al., 1994) and more recent studies documenting the undertreatment of cancer pain in older people (Bernabei et al., 1998; Gao, Gulliford, & Higginson, 2011; Higginson & Gao, 2012; Yun et al., 2004). Interestingly, there were subtle age-related patterns in the relationships of treatment factors to pain interference. In the regression model for younger, but not older people, taking more analgesics of any class was associated with greater pain interference, while in in the regression model for older, but not younger people, receipt of an opioid prescription was associated with greater pain interference. Although previous studies have identified associations between healthcare provider treatment choices and patient age (Green, Wheeler, & LaPorte, 2003; McCaffery & Ferrell, 1991), this is the first study to document these subtle age-related treatment differences within people with cancer pain. One possible explanation may be that there are age-related patterns in healthcare providers' responses to outward displays or reports of pain-related impairment. In older people, who may be less likely than younger people to be prescribed an opioid, greater pain interference may be an important factor in the decision to prescribe an opioid, while in younger people, greater pain interference may be associated with provision of more analgesic treatment overall. This

might suggest that healthcare providers may act on cues about the impact of pain differently in older than younger people. Patient-related barriers to treatment may also be relevant, such as fears of addiction and the beliefs that good patients do not complain about pain and that reporting pain may distract healthcare providers from cancer treatment (Ward et al., 1993). Future research is needed to investigate whether greater displays or reports of pain interference elicit somewhat different treatment based on age, as this may have important implications for improving the undertreatment of cancer pain in older people.

Comorbidity was less common in younger than older patients. However, younger patients with comorbidities experienced worse non-neuropathic sensory pain qualities than younger patients without comorbidities. In contrast, in the regression models for older patients, comorbidity did not emerge as an important correlate of any of the pain outcomes. Age-related patterns in the impact of comorbidities on the experience of cancer pain have received limited attention to-date. In one study, comorbidity was associated with lower activity restriction in younger than older people (G. M. Williamson & Schulz, 1995). Unfortunately, a nonvalidated measure of comorbidity was used; therefore, it is difficult to integrate these findings. While comorbidity is associated with increasing age (Dominick, Blyth, & Nicholas, 2012; Extermann, 2000b), it is not exclusively a problem of older people. However, studies of comorbidity in people with cancer and chronic nonmalignant pain have largely focused on older, rather than younger people and have excluded younger people altogether (Blyth et al., 2008; Extermann, 2000a; C. W. Given, Given, Azzouz, Kozachik, & Stommel, 2001; Leong, Farrell,

Helme, & Gibson, 2007; Yancik, Ganz, Varricchio, & Conley, 2001). Consequently, our understanding of the impact of comorbidity on younger people with cancer pain has remained limited. The present data suggest that comorbidity may put younger people at risk for poor cancer pain outcomes and that this factor should not be ignored when assessing cancer pain and its impact in younger people.

Moreover, although there were no age differences in the proportion of older and younger people with chronic nonmalignant pain, this health status factor was associated with greater non- neuropathic pain qualities for older, but not younger patients. Chronic nonmalignant pain has been identified as a risk factor for the undertreatment of cancer pain (Valeberg, Rustoen et al., 2008), but this is the first study to identify chronic nonmalignant pain as a risk factor for poor pain outcomes specifically in older cancer patients. These results demonstrate that future studies of people with cancer pain should also assess the presence and impact of chronic nonmalignant as it may represent a risk factor for poor cancer pain outcomes among older people.

There was also an age-related pattern in the relationship of physical health quality of life and pain outcomes. In younger patients it was associated with lower pain interference, and non-neuropathic and neuropathic pain qualities. In contrast, in older patients, while it was associated with lower neuropathic pain qualities, it was not associated with non-neuropathic pain qualities or pain interference. These data complement and extend findings from an earlier study which demonstrated that despite a lack of age differences in perceptions of global health QOL and pain intensity, the

correlation between these two factors was stronger in younger than older postoperative patients (Mangione et al., 1993).

Additionally, although two other health status factors – functional status and cancer symptom severity – were common correlates of pain outcomes in both older and younger patients, there was evidence of age-related patterns in their role in the relationship between pain catastrophizing and pain interference. In older, but not younger patients, cancer symptom severity and functional status acted as a suppressor of this relationship, changing the direction of the relationship from positive, which has been consistently demonstrated (Hanley, Raichle, Jensen, & Cardenas, 2008; Hirsh, Bockow, & Jensen, 2011; Sullivan, Thorn, Haythorntwaite, Keefe, Martin, Bradley, & Lefebvre, 2001), to negative. The Communal Coping Model of Catastrophizing (CCM) suggests that catastrophizing is enacted to elicit support (Sullivan, Thorn, Haythorntwaite, Keefe, Martin, Bradley, & Lefebvre, 2001). There is emerging support for this model in people with chronic nonmalignant pain (Buenaver, Edwards, & Haythornthwaite, 2007; Cano, 2004; Giardino, Jensen, Turner, Ehde, & Cardenas, 2003; Pence, Cano, Thorn, & Ward, 2006). In people with cancer pain, catastrophizing has been associated with tangible, but not emotional support (Keefe et al., 2003). We have also demonstrated that catastrophizing is related to more frequently perceived solicitous and distracting support with a smaller subset of this sample (Gauthier et al., 2012). The present data suggest that the communication value of catastrophizing may be age-related: older people with severe cancer symptomatology and impaired functional status may experience a unique supportive context that is not available to younger people. In support of this idea, while

older people with advanced cancer described strengthened relationships as a result of pain, younger people described relational strain, and that their partners did not understand their pain (Gagliese et al., 2009). Although very preliminary, these intriguing findings require further investigation.

Taken together, it appears that there are certain health status factors that are uniquely important to cancer pain outcomes based on age group, like comorbidities in younger patients and chronic nonmalignant pain in older patients, while other factors, like physical health quality of life, cancer symptom severity and functional status, are important to pain outcomes in both age groups, but in somewhat different ways. Through the investigation of relationships between multiple measures of health status and multidimensional pain outcomes, we have uncovered a much more comprehensive profile of risk factors for cancer pain in older and younger patients than has been available previously. Future studies should incorporate these details in order to fully understand the complex nature of the relationships between multidimensional pain outcomes and health status across the adult life span.

It has been suggested that older people are less psychologically affected by cancer than younger people (Blank & Bellizzi, 2008) and some studies of cancer patients that do not consider pain have found older age to be associated with fewer depressive symptoms or less distress (Compas et al., 1999; Kroenke et al., 2004; Mosher & Danoff-Burg, 2005; Lo et al., 2010; Politi, Enright, & Weihs, 2007; Schroevers, Ranchor, & Sanderman, 2004; Vinokur, Threatt, Vinokur-Kaplan, & Satariano, 1990; Wenzel et al., 1999). We did not find support for this suggestion in the context of cancer pain: A similar proportion

of older and younger patients scored above cutoffs for clinically-relevant distress on measures of depressive symptoms and traumatic distress, and more than half of older and younger patients reported depressive symptoms in a range suggestive of possible clinical depression (Radloff, 1977). Moreover, depressive symptoms were associated with neuropathic pain in older and younger patients, suggesting that, in both age groups, interventions designed to alleviate neuropathic pain may be equally important for improving distress, and vice versa, interventions designed to alleviate distress may be equally important for improving neuropathic pain. However, consistent with previous studies (Butler, Koopman, Classen, & Spiegel, 1999; Hart et al., 2012; Schroevers, Ranchor, & Sanderman, 2004; J. Turner, Kelly, Swanson, Allison, & Wetzig, 2005), older patients had fewer intrusive thoughts than younger patients. More interestingly, in the regression models, intrusion was associated with greater pain intensity, non-neuropathic sensory pain qualities, and interference in younger but not older patients. In a qualitative study, more younger than older patients described "waiting to live". They reacted to the loss of their pre-pain identities and activities with anger and grief and described feeling overwhelmed by pain (Gagliese et al., 2009), reactions which may be related to intrusive thoughts about the experience of cancer pain. In contrast, more older than younger patients described "living despite pain" (Gagliese et al., 2009) . They discussed the importance of maintaining their activities and refusing to let pain control their lives.

Together with that study (Gagliese et al., 2009) , and previous research demonstrating age-related patterns in adaptation to chronic illness (Aldwin, Sutton,

Chiara, & Spiro, 1996; Diamond & Aspinwall, 2003; Felton & Revenson, 1987; Stanton, Revenson, & Tennen, 2007) these findings suggest that the adaptive value of prior health limitations may differ across the adult life span (Gagliese et al., 2009). Although older people may be faced with a constellation of factors which may be associated with vulnerability to negative pain outcomes (Davis & Srivastava, 2003; Extermann, 2000a; Mercadante, Casuccio, Pumo, & Fulfaro, 2000; Yancik & Ries, 2000), the experience of adapting to comorbidities may be associated with a unique repertoire of accommodative strategies whose development may be facilitated by observing age-related health limitations among peers (Gagliese et al., 2009; Schulz & Heckhausen, 1996). A related explanation may be response shift or cognitive reappraisal (Diamond & Aspinwall, 2003; Stanton, Revenson, & Tennen, 2007), which suggest that adaptation to other chronic conditions may result in a recalibration of responses on self-report measures (Daltroy, Larson, Eaton, Phillips, & Liang, 1999; Ubel, Jankovic, Smith, Langa, & Fagerlin, 2005). In contrast, among younger people, cancer pain may be inconsistent with normative health expectations, and may be perceived as threatening to future life goals (Gagliese et al., 2009). Rather than providing an adaptive advantage, the presence of comorbidities along with cancer pain may instead represent further lifecourse violations and additional vulnerability to poor outcomes. Taken together with the qualitative study described above (Gagliese et al., 2009), it is possible that there are age-related patterns in the cognitive-affective dimension of cancer pain. In further support of this possibility, pain-related cognitive anxiety was associated with greater pain interference in older, but not younger people. Intriguingly, it was correlated with greater pain intensity only in older patients.

This is the first study to document this age-related pattern in the relationship between pain-related cognitive anxiety and cancer pain outcomes.

Despite the age-related patterns in the cognitive-affective dimension noted above, pain willingness, an element of pain acceptance (McCracken, 1998) which may represent another component of this dimension, was a common correlate of pain outcomes across both age groups. Pain acceptance has been related to lower pain intensity and better physical and psychosocial wellbeing in people with chronic nonmalignant pain (McCracken & Eccleston, 2005; McCracken, 2005a; McCracken, 2005b; McCracken & Eccleston, 2006; Viane et al., 2003). In a smaller subset of this sample, we found that pain willingness was related to lower pain catastrophizing as well as parental status, which may have operated as a proxy for life stage (Gauthier et al., 2009). Specifically, parents living with children had much lower pain willingness than people who were not parents. In the qualitative study described above, more older than younger people with cancer pain described acceptance as an important method of positive adaptation to pain (Gagliese et al., 2009). Based on the present findings, it is possible that enhancing patients' willingness to accept pain while encouraging letting go of futile efforts to control pain would be important to improving pain and wellbeing regardless of age or life stage.

Although the individual correlates differed slightly, most of the regression models demonstrated that physical and psychological factors were associated with pain outcomes in both older and younger patients. There were two noteworthy findings that emerged with regard to the models predicting neuropathic pain. First, depressive symptoms

emerged as a correlate of neuropathic pain, but not other pain outcomes. This is surprising, given the extensive literature demonstrating the relationship between depression and cancer pain (Laird, Boyd, Colvin, & Falon, 2009). Although some studies have attempted to compare psychological wellbeing in cancer patients with nociceptive and neuropathic pain (Burrows, Dibble, & Miaskowski, 1998; Tofthagen& McMillan, 2010; Wilkie et al., 2001), the findings have been mixed and age-related patterns in these relationships have not been evaluated. It is difficult to integrate the inconsistent findings due to the wide variation in classification criteria for neuropathic pain across studies. One possible explanation may be that neuropathic pain is highly distressing regardless of life stage because it may be refractory to treatment (Dworkin et al., in press; Mercadante & Portenoy, 2001). Future studies should investigate differences in the biopsychosocial predictors of neuropathic and nociceptive cancer pain using validated methods. The second noteworthy finding relates to the age-related pattern that emerged in the profile of correlates of neuropathic pain. Although physical health QOL and depressive symptoms emerged for both age groups, disease duration, receipt of an opioid, and symptom severity emerged for younger, but not older patients. We have shown that the psychometric properties of the SF-MPQ-2 are not age-related (Chapter 2), therefore these findings are likely not due to age differences in the psychometric properties of the measure. Future studies investigating age-related patterns in the psychosocial correlates of neuropathic pain are warranted.

To date, much of the literature describing age-related patterns in cancer pain has been hindered by methodological limitations, narrow scope in the operationalization of

cancer pain, and a persistent reliance on the biomedical model. With the aging population (Statistics Canada, 2007), it is increasingly important to improve our understanding in order to enhance pain palliation for adults across the life span. A recent literature review of older people's experience of cancer pain concluded that the existing literature is "scant and heterogeneous" (Dunham, Ingleton, Ryan, & Gott, 2013, p. 2108). Unfortunately, this review excluded younger people, and therefore did not contribute to an improved understanding of the experience of cancer pain across the adult life span. By excluding younger people, we have no idea whether the "themes" uncovered by the authors are unique among older people and should therefore guide the development of treatments tailored to older people, or if these are common experiences to older and younger people. The present study provides important evidence describing the experience of cancer pain across the adult life span. In summary, although there were no age differences in cancer pain, older people were somewhat less likely than younger people to receive an opioid and there were age differences in the relationship of treatment factors and pain interference. We identified a number of unique health status risk factors for older and younger patients as well as a possible unique role of health status factors in the relationship between catastrophizing and pain interference for older but not younger patients, which may represent age-related patterns in the supportive context of cancer pain. Finally, although a similar number of older and younger patients reported levels of distress indicative of clinically relevant symptomatology, age-related patterns in the relationships of intrusive thoughts and pain outcomes may be suggestive of a unique adaptive advantage of some health status factors in older but not younger patients.

This study improves on the methodological limitations of the existing literature in a number of ways. First, the inclusion criteria of people reporting cancer pain prevented confounding prevalence with intensity. Second, the measure of pain qualities is valid for use across the adult life span (Chapter 2), which increases confidence in our interpretation of age-related patterns as actual patterns, and not age differences in the psychometric properties of the scale. Third, the matching procedure used in this study is a particular strength. No prior studies of age-related patterns in cancer pain have matched participants on sex and primary tumor type. This is important, as these factors have been associated with cancer pain (Dobratz, 2008; Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009; Grond, Zech, Diefenbach, Radbruch, & Lehmann, 1996; Miaskowski, 2004; Vainio & Auvinen, 1996). Despite these important strengths, there are several limitations which must be taken into account when interpreting the findings. The majority of participants were well-educated, predominantly Caucasian patients receiving specialized symptom management at a comprehensive tertiary cancer care centre (Chapter 2). Additionally, those who completed the questionnaires were younger and had better functional status than those who failed to return the questionnaires. Although poor performance status is often associated with withdrawal from studies (Garland, Carlson, Marr, & Simpson, 2009; Gilbertson-White, Aouizerat, Jahan, & Miaskowski, 2011; Hardy, Allore, & Studenski, 2009; Mody et al., 2008; Ransom, Azzarello, & McMillan, 2006), future studies should endeavor to include older people with severe functional impairments who are not receiving specialized symptom management. The cross-sectional design of this study precludes statements of causality.

Longitudinal studies are required to assess the trajectory of pain and its correlates in older and younger patients as they approach the end of life.

A number of significant future research directions are evident based on the results of this study. First, cancer pain is dynamic and may fluctuate with treatment changes or as the disease progresses. The health status factors that operated differently in older and younger patients may be impacted by disease progression (Harris et al., 2013; Kang, Kwon, Hui, Yennurajalingam, & Bruera, 2013; Visovsky, Berger, Kosloski, & Kercher, 2008), by the process of aging (B. Chen, Covinsky, Stijacic Cenzer, Adler, & Williams, 2012; Inouye, Studenski, Tinetti, & Kuchel, 2007; Miller, Longino, Anderson, James, & Worley, 1999), or by an interactive process of disease progression and aging (Dale et al., 2012), and may therefore impact on pain outcomes differently over time in older and younger patients. Longitudinal studies of age-related patterns in cancer pain that consider these factors are necessary. Second, studies that include caregivers are necessary to investigate the possibility of a unique supportive context in older patients, especially those who are burdened by severe cancer symptoms and compromised functional status. These studies would provide important information about caregivers' supportive responses to older and younger patients' catastrophizing, based on patients' symptom severity and functional status. Since receipt of an opioid was associated with greater pain interference, it might be possible that the presence of a unique supportive context that mitigates pain interference may also have implications for the receipt of analgesia among older people. Vignette studies with healthcare providers may be useful to test this

possibility (Burgess, van Ryn, Crowley-Matoka, & Malat, 2006; Green, Wheeler, & LaPorte, 2003; McCaffery & Ferrell, 1991; Weisse, Sorum, Sanders, & Syat, 2001).

In the end, the age differences uncovered in this study were subtle. Importantly, despite the fact that older people were somewhat less likely than younger people to receive an opioid, may experience a unique supportive context, and may adapt differently based on experience with certain health limitations, cancer pain was equally distressing in both age groups. It felt the same, hurt just as much, and interfered in important aspects of daily living to the same extent in older and younger patients. As a result, there is no reason to think that older people are less affected by cancer pain than younger people. These data have heuristic and clinical value. They will contribute to future studies that will further refine the biopsychosocial model of cancer pain across the adult life span. They will also contribute to studies that will and design and test interventions tailored to the unique needs of older and younger people. These studies are urgently needed in order to reduce suffering at the end of life in adults of all ages.

Table 1. Study measures by age group

	Mean ± SD; N (%)			
	Total (n=244)	Younger (n=139)	Older (n=105)	$P \leq$
BPI Average Pain Intensity	3.82 ± 2.02	4.00 ± 2.12	3.70 ± 2.12	.28
BPI Pain Interference	4.82 ± 2.41	4.93 ± 2.37	4.67 ± 2.48	.40
PMI < 0	36 (14.8)	19 (13.7)	17 (16.2)	.58
SF-MPQ-2 Continuous	3.29 ± 2.16	3.39 ± 2.15	3.15 ± 2.17	.38
SF-MPQ-2 Intermittent	2.47 ± 2.30	2.67 ± 2.43	2.20 ± 2.12	.11
SF-MPQ-2 Neuropathic	1.93 ± 1.73	2.06 ± 1.81	1.76 ± 1.60	.18
SF-MPQ-2 Affective	2.79 ± 2.33	2.94 ± 2.32	2.59 ± 2.35	.25
SF-MPQ-2 Total	2.59 ± 1.74	2.74 ± 1.74	2.39 ± 1.72	.12
ESAS Physical symptoms	4.03 ± 1.74	3.99 ± 1.69	4.08 ± 1.82	.68
SF-36 PHC	29.19 ± 7.58	29.03 ± 7.39	29.40 ± 7.86	.71
SF-36 MHC	43.45 ± 11.04	42.83 ± 10.54	44.28 ± 11.66	.31
CES-D	20.86 ± 10.56	21.60 ± 10.15	19.89 ± 11.06	.21
IES Avoidance	13.40 ± 9.01	13.72 ± 9.41	12.99 ± 8.47	.53
IES Intrusion	10.66 ± 7.86	12.24 ± 7.99	8.58 ± 7.21	.0001
IES Total	24.07 ± 15.24	25.96 ± 15.75	21.56 ± 14.23	.03
PAQ-C Stoicism	3.04 ± 0.81	3.02 ± 0.85	3.07 ± 0.76	.64
PAQ-C Cautiousness	2.39 ± 0.93	2.28 ± 0.88	2.53 ± 0.99	.04

CPAQ Activity Engagement	34.14 ± 12.58	33.50 ± 12.91	34.98 ± 12.14	.37
CPAQ Pain Willingness	21.45 ± 9.65	21.58 ± 9.60	21.29 ± 9.76	.82
CPAQ Total	55.59 ± 18.14	55.08 ± 19.10	56.27 ± 16.86	.61
PASS-20 Fear	8.65 ± 5.72	9.04 ± 5.43	8.13 ± 6.06	.22
PASS-20 Escape-Avoidance	13.37 ± 5.66	13.78 ± 5.59	12.84 ± 5.75	.20
PASS-20 Physiological Anxiety	6.97 ± 5.24	7.20 ± 4.97	6.65 ± 5.58	.42
PASS-20 Cognitive Anxiety	13.33 ± 6.15	14.02 ± 5.91	12.42 ± 6.37	.04
PASS-20 Total	42.32 ± 19.32	44.05 ± 17.90	40.03 ± 20.92	.11
PCS Rumination	7.54 ± 4.40	7.56 ± 4.26	7.52 ± 4.59	.94
PCS Magnification	4.04 ± 3.04	3.93 ± 2.91	4.18 ± 3.22	.53
PCS Helplessness	8.41 ± 5.80	8.36 ± 5.51	8.49 ± 6.19	.87
PCS Total	20.00 ± 12.09	19.86 ± 11.41	20.19 ± 12.98	.83
FACIT-Sp-12 Meaning-Peace	22.49 ± 6.82	22.45 ± 6.36	22.55 ± 7.41	.91
FACIT-Sp-12 Faith	8.97 ± 5.04	8.60 ± 5.06	9.47 ± 4.98	.18
FACIT-Sp-12 Total	31.47 ± 9.84	31.05 ± 9.62	32.02 ± 10.15	.44
MPI Punishing Responses	1.07 ± 1.26	1.12 ± 1.27	1.00 ± 1.27	.48
MPI Solicitous Responses	4.54 ± 1.22	4.59 ± 1.16	4.48 ± 1.29	.48
MPI Distracting Responses	2.94 ± 1.38	2.85 ± 1.39	3.04 ± 1.37	.30
MOS-SS # of Close Friends and Relatives	6.61 ± 4.79	6.59 ± 4.28	6.63 ± 5.41	.96

MOS-SS Emotional Information	80.46 ± 19.97	80.99 ± 19.39	79.77 ± 20.77	.64
MOS-SS Tangible	79.25 ± 23.52	79.85 ± 22.16	78.46 ± 25.29	.65
MOS-SS Affectionate	86.17 ± 21.59	86.36 ± 21.43	85.92 ± 21.91	.88
MOS-SS Positive Social Interaction	80.84 ± 21.13	81.50 ± 20.29	79.98 ± 22.27	.58
MOS-SS Total	80.99 ± 19.06	81.51 ± 18.87	80.31 ± 19.38	.63
ECR Avoidance	3.10 ± 1.01	3.11 ± 1.05	3.10 ± 0.97	.94
ECR Anxiety	2.48 ± 1.06	2.55 ± 1.11	2.38 ± 0.99	.20
KMS Total (n=176)	18.43 ± 3.81	18.27 ± 3.76	18.64 ± 3.90	.54

Notes. BPI, Brief Pain Inventory, PMI, Pain Management Index, SF-MPQ-2, Short-Form McGill Pain Questionnaire 2; ESAS, Edmonton Symptom Assessment Scale; SF-36 PHC, SF-36 Physical Health Component Summary Score; SF-36 MHC, SF-36 Mental Health Component Summary Score; CES-D, Center for Epidemiologic Studies-Depression Scale; IES Impact of Event Scale; PAQ-C, Pain Attitudes Questionnaire, CPAQ, Chronic Pain Acceptance Questionnaire; PASS-20, Short Form Pain Anxiety Symptoms Scale; PCS, Pain Catastrophizing Scale; FACIT-Sp 12, Functional Assessment of Chronic Illness Therapy – Spiritual Wellbeing 12; MPI, Multidimensional Pain Inventory; MOS-SS, Medical Outcomes Study Social Support Survey; ECR, Experiences in Close Relationships Inventory; KMS, Kansas Marital Satisfaction Scale; SD, Standard Deviation

Table 2. Candidate correlates of each outcome variable (n=244).

	BPI Average Pain Intensity	BPI Pain Interference	SF-MPQ-2 Continuous	SF-MPQ- 2 Intermittent	SF-MPQ- 2 Neuropathic	SF-MPQ-2 Affective
Age (years)	.006	-.010	-.064	-.071	-.086	-.034
Sex	-.082	-.121	-.046	-.138	-.118	-.131
English primary language	-.140	-.133	-.046	-.145	-.098	-.123
Marital Status	.009[f]	-.027[f]	-.012[f]	.025[f]	-.040[f]	-.035[f]
Education	-.027[f]	-.109[f]	-.021[f]	-.009[f]	.027[f]	-.075[f]
BMI	.101	.064	.095	.151	.141	.047
Primary tumor type ‖	.874	1.079	.937	.814	.826	.448
Cancer duration (months)	.068	.069	.116	.071	**.206****	.123
Pain duration (months)	-.049	.030	.055	.016	.126	.139
Chronic Non-Cancer Pain	.110	.060	**.206****	**.179***	.121	.155
Count analgesics taken	.063	**.174****	.104	.050	.103	.097

Polypharmacy	.085	.107	.052	.061	.036	.112
ADS	.124	.136	**.166***	.141	.034	**.151***
Chemotherapy, Radiation or Hormone treatment	**-.238****	-.154	**-.180***	-.155	-.064	-.146
Non-pharmacological pain treatment	-.065	-.049	-.030	-.032	-.036	-.050
Prescribed an opioid	.036[f]	.142[f]	.064[f]	.092[f]	-.024[f]	.104[f]
CCI >0	.090[f]	.016[f]	.131[f]	.100[f]	.006[f]	.064[f]
KPS	-.216**[f]	-.372**[f]	-.269**[f]	-.266**[f]	-.157*[f]	-.280**[f]
BPI Average pain intensity	1	.598**	.568**	.473**	.489**	.494**
BPI Interference	.598**	1	.510**	.504**	.456**	.596**
SF-MPQ-2 Continuous	.568**	.510**	1	.575**	.581**	.675**
SF-MPQ-2 Intermittent	.473**	.504**	.575**	1	.578**	.595**
SF-MPQ-2 Neuropathic	.489**	.456**	.581**	.578**	1	.555**

SF-MPQ-2 Affective	.494**	.596**	.675**	.595**	.555**	1
ESAS Physical symptoms	**.326****	**.502****	**.350****	**.289****	**.328****	**.496****
SF-36 PHC	**-.220****	**-.395****	**-.265****	**-.327****	**-.219****	**-.227****
SF-36 MHC	-.149*b	-.335**b	-.136*b	-.110	-.179**b	-.356**b
CES-D	**.245****	**.358****	**.208****	**.206****	**.326****	**.392****
IES Avoidance	.157	.219**c	.062	.205**c	.155	.244**
IES Intrusion	.176*f	.292**f	.180*f	.210**f	.254**f	.381**f
PAQ-C Stoicism	.061	.001	.078	.115	.146	.090
PAQ-C Cautiousness	-.028f	.063f	-.009f	.040f	.064f	.100f
CPAQ Activity Engagement	-.155	**-.349****	-.072	-.112	-.060	-.155
CPAQ Pain Willingness	**-.160****	**-.281****	-.152	**-.237****	**-.188***	**-.313****
PASS-20 Fear	.192*d	.298**d	.184*d	.144	.265**d	.403**d
PASS-20 Escape-Avoidance	.063	.235**d	.072	.163	.124	.193*d

PASS-20 Physiological Anxiety	.176^{*d}	.342^{**d}	.174^{*d}	.177^{*d}	.284^{**d}	.321^{**d}
PASS-20 Cognitive Anxiety	.154^{f}	.335$^{** f}$	.177$^{* f}$	.220$^{** f}$	.210$^{** f}$	.313$^{** f}$
PCS Rumination	.217^{**e}	.306^{**e}	.155	.276^{**e}	.291^{**e}	.384^{**e}
PCS Magnification	.186^{*e}	.224^{**e}	.185^{*e}	.174^{*e}	.207^{**e}	.401^{**e}
PCS Helplessness	.244^{**e}	.326^{**e}	.189^{*e}	.256^{**e}	.319^{**e}	.420^{**e}
PCS Total	**.243****	**.324****	**.194***	**.267****	**.311****	**.442****
FACIT-Sp-12 Mean/Peace	-.213^{**b}	-.279^{**b}	-.085	-.147	-.163	-.218^{**b}
FACIT-Sp-12 Faith	-.031	.010	.080	-.043	.089	.127*
MPI Punishing	.063	.139	.115	.098	**.185***	.067
MPI Solicitous	.028	.081	.122	.034	-.033	.118
MPI Distracting	.001	-.070	.091	.005	.073	.110
MOS-SS Average # family/friends	-.089	-.056	-.018	-.058	-.090	.007

MOS-SS Emotional Information	-.083	-.075	-.032	-.062	-.083	-.064
MOS-SS Tangible	-.036	-.034	-.006	-.021	-.014	-.019
MOS-SS Affectionate	-.058	-.095	-.044	-.100	-.122	-.035
MOS-SS Positive Social Interaction	-.055	-.113	.006	-.053	-.081	-.069
ECR Avoidance	.121	.153	.069	.064	.125	.129
ECR Anxiety	.066	**.173***	.095	**.177***	**.186***	**.262****
KMS	-.077	-.079	-.043	.074	-.033	.040

Values are Pearson's Correlation coefficients or Spearman's Rho

* $p \leq .01$; ** $p \leq .001$, bolded coefficients were retained for inclusion in the Multivariate models in the second step of correlate selection.

Notes. BPI, Brief Pain Inventory; SF-MPQ-2, Short-Form McGill Pain Questionnaire 2; IES Impact of Event Scale; ADS, Anticholinergic Drug Scale; CCI, Charlson Comorbidity Index; KPS, Karnofsky Performance Status Scale; ESAS, Edmonton Symptom Assessment Scale; SF-36 PHC, SF-36 Physical Health Component Summary Score; SF-36 MHC, SF-36 Mental Health Component Summary Score; CES-D, Center for Epidemiologic Studies-Depression Scale; PAQ-C, Pain Attitudes

Questionnaire, CPAQ, Chronic Pain Acceptance Questionnaire; PASS-20, Short Form Pain Anxiety Symptoms Scale; PCS, Pain Catastrophizing Scale; FACIT-Sp 12, Functional Assessment of Chronic Illness Therapy – Spiritual Wellbeing 12; MPI, Multidimensional Pain Inventory; MOS-SS, Medical Outcomes Study Social Support Survey; ECR, Experiences in Close Relationships Inventory; KMS, Kansas Marital Satisfaction Scale; SD, Standard Deviation

[a] Not retained for inclusion. Correlations with BPI Average Pain Intensity ≥.6

[b] Not retained for inclusion. Correlation with CES-D ≥.6

[c] Not retained for inclusion. Correlation with IES Intrusion ≥.6

[d] Not retained for inclusion. Correlations with PASS-20 Cognitive Anxiety ≥.6

[e] PCS subscale intercorrelations ≥.6 therefore PCS Total retained for inclusion.

[f] All multivariate models included the variables that differed between older and younger patients at $p \leq .05$.

‖ F-test statistic

Table 3. Summary chart of significant ($p \leq .05$) correlates retained in each final multivariate regression model

	Post-grad degree	Chronic NMP	CCI > 0	KPS	Cancer dur	# pain meds taken	Rx opioid	CTX/ RT/H T	ESAS Phys sx	SF-36 PHC	CES-D	IES Intrus	CPAQ PW	PCS Tot	PASS-20 Cog Ax
	Y O	Y O	Y O	Y O	Y O	Y O	Y O	Y O	Y O	Y O	Y O	Y O	Y O	Y O	Y O
BPI Avg PI	+		+	—				— —	+ +			+	—		—
SF-MPQ-2 Cont		+	+	—				—	+	—		+			
SF-MPQ-2 Inter	+		+	—					+	—		+	—		
SF-MPQ-2 NeP					+		—		+	— —	+ +				
SF-MPQ-2 Aff				—					+ +			+ +	—	+	
BPI Int	—			— —		+	+		+ +	—		+		+ —	+

Notes: BPI Avg PI, BPI Average Pain Intensity; SF-MPQ-2 Cont, Inter, NeP, Aff, SF-MPQ-2 Continuous, Intermittent, Neuropathic, Affective; BPI Int, BPI Interference; Post-grad degree, post-graduate degree; Chronic NMP, Chronic nonmalignant pain; CCI, Charlson Comorbidity Index; KPS, Karnofsky Performance Status Scale; Cancer dur, Cancer duration; # pain meds taken, count of analgesics taken; Rx opioid, prescribed an opioid; CTX/RT/HT, chemotherapy, radiation

or hormone treatment; ESAS Phys sx, Edmonton Symptom Assessment Scale Physical symptom severity; SF-36 PHC, SF-36 Physical Health Component Score; CES-D, Center for Epidemiologic Studies – Depression scale; IES Intrus, Impact of Events Scale Intrusion; CPAQ PW, Chronic Pain Acceptance Questionnaire Pain Willingness subscale; PCS Tot, Pain Catastrophizing Scale Total; PASS-20 Cog Ax, Pain Anxiety Symptoms Scale-short form Cognitive Anxiety subscale; Y, Younger; O, Older; +, positive relationship; —, negative relationship.

Table 4. Multivariate linear regression correlates of Brief Pain Inventory Average Pain Intensity

	Younger		Older		
	B (SE)	**β**	**B (SE)**	**β**	**SE b-diff**
Post-graduate degree [a]			1.743(.481)	.298***	
CCI >0	.800 (.396)	.163*			
KPS			-.040(.018)	-.199*	
Chemotherapy/ radiation/ hormone therapy	-.922 (.337)	-.214**	-1.677 (.340)	-.398***	1.576
ESAS Physical symptoms	.275 (.107)	.219**	.219 (.107)	.188***	.370
CPAQ Pain Willingness	-.057 (.020)	-.260**			
IES Intrusion	.050(.023)	.088*			
PASS-20 Cognitive Anxiety	-.069 (.035)	-.192*	.053 (.028)	.159	.005**
	$F_{(6,132)} = 6.260, p \leq .0001$, $R^2 = .222$; Adjusted $R^2 = .186$		$F_{(5,99)} = 12.870, p \leq .0001$, $R^2 = .394$; Adjusted $R^2 = .363$		

[a] reference category is ≤ High School; SE b–diff = SE b-difference; CCI, Charlson Comorbidity Index; KPS, Karnofsky Performance Status Scale; ESAS, Edmonton Symptom Assessment Scale; CPAQ, Chronic Pain Acceptance Questionnaire; IES, Impact of Events Scale; PASS-20, Pain Anxiety Symptoms Scale-short form

* $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

Table 5. Multivariate linear regression correlates of Short-Form McGill Pain Questionnaire-2 Continuous pain qualities

	Younger		Older		
	B (SE)	**β**	**B (SE)**	**β**	**SE b-diff**
Chronic nonmalignant pain			.887 (.395)	.189*	
CCI >0	1.227 (.389)	.246**			
KPS	-.050 (.017)	-.238**			
Chemotherapy/ radiation/ hormone therapy	-.604 (.334)	-.138	-1.040 (.363)	-.240**	.495
ESAS Physical symptoms			.516 (.100)	.432***	
SF-36 PHC	-.050 (.023)	-.173*			
IES Intrusion	.058 (.021)	.216**			
	$F_{(5,133)} = 8.502, p \leq .0001$, R^2=.242; Adjusted R^2 = .214		$F_{(3,101)} = 13.929, p \leq .0001$, R^2=.293; Adjusted R^2 = .272		

SE b–diff = SE b-difference; CCI, Charlson Comorbidity Index; KPS, Karnofsky Performance Status Scale; ESAS, Edmonton Symptom Assessment Scale; SF-36 PHC, SF-36 Physical Health Component Score; IES, Impact of Events Scale;

* $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

Table 6. Multivariate linear regression correlates of Short-Form McGill Pain Questionnaire-2 Intermittent pain qualities

	Younger		Older		
	B (SE)	**β**	**B (SE)**	**β**	**SE b-diff**
Post-graduate degree [a]	1.046 (.471)	.166*			
Chronic nonmalignant pain			.763 (.488)	.166	
CCI >0	1.087 (.427)	.193 **			
KPS	-.054 (.018)	-.226 **			
ESAS Physical symptoms			.308 (.108)	.264**	
SF-36 PHC	-.101 (.025)	-.309***			
CPAQ Pain Willingness			-.054 (.020)	-.250**	
IES Intrusion	.060 (.023)	.196**			
	$F_{(5,133)} = 10.641$, $p \leq .0001$, R^2=.286; Adjusted R^2 = .259		$F_{(3,101)} = 8.740$, $p \leq .0001$, R^2 = .206; Adjusted R^2 = .183		

[a] reference category is ≤ High School; SE b–diff = SE b-difference;

CCI, Charlson Comorbidity Index; KPS, Karnofsky Performance Status Scale; ESAS, Edmonton Symptom Assessment Scale; SF-36 PHC, SF-36 Physical Health Component Score; CPAQ, Chronic Pain Acceptance Questionnaire; IES, Impact of Events Scale;

* $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

Table 7. Multivariate linear regression correlates of Short-Form McGill Pain Questionnaire-2 Neuropathic pain qualities

	Younger		Older		
	B (SE)	**β**	**B (SE)**	**β**	**SE b-diff**
Cancer duration (months)	.013 (.003)	.289***	.005(.003)	.174	.004*
Prescribed an opioid	-1.515 (.595)	-.189**			
ESAS Physical symptoms	.225 (.092)	.209*			
SF-36 PHC	-.040 (.018)	-.166*	-.044 (.019)	-.219*	.026
CESD	.049 (.014)	.276***	.039 (.013)	.273**	.019
MPI Punishing Responses	.208 (.107)	.146			
	$F_{(6,124)} = 10.490, p \leq .0001$, $R^2 = .337$; Adjusted $R^2 = .305$		$F_{(3,100)} = 6.580, p \leq .0001$, $R^2 = .165$; Adjusted $R^2 = .140$		

SE b–diff = SE b-difference; ESAS, Edmonton Symptom Assessment Scale; SF-36 PHC, SF-36 Physical Health Component Score; CES-D, Center for Epidemiologic Studies – Depression scale; MPI, Multidimensional Pain Inventory;

* $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

Table 8. Multivariate linear regression correlates of Short-Form McGill Pain Questionnaire-2 Affective pain qualities

	Younger		Older		
	B (SE)	**β**	**B (SE)**	**β**	**SE b-diff**
KPS	-.037 (.016)	-.162*			
ADS	.124 (.070)	0.127			
ESAS Physical symptoms	.319 (.108)	.233**	.514 (.110)	.399***	.154
SF-36 PHC			-.046 (.024)	-.152	
CPAQ Pain Willingness			-.045 (.020)	-.186*	
PCS Total	.056 (.016)	.279***			
IES Intrusion	.047 (.023)	.163*	.076 (.028)	.231**	.036
	$F_{(5,133)} = 15.135, p \leq .0001$, $R^2 = .363$; Adjusted $R^2 = .339$		$F_{(4,100)} = 19.082, p \leq .0001$, $R^2 = .433$; Adjusted $R^2 = .410$		

SE b–diff = SE b-difference; ESAS, Edmonton Symptom Assessment Scale; SF-36 PHC, SF-36 Physical Health Component Score; CPAQ PW, Chronic Pain Assessment Questionnaire; PCS, Pain Catastrophizing Scale; IES, Impact of Events Scale; * $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

Table 9. Multivariate linear regression correlates of Brief Pain Inventory Pain Interference

	Younger		Older		
	B (SE)	**β**	**B (SE)**	**β**	**SE b-diff**
Post-secondary [a]	-.657 (.364)	-.139			
Post-graduate degree [a]	-.954 (.472)	-.155*			
KPS	-.038 (.017)	-.158**	-.056 (.019)	-.236**	.025
Count analgesics taken	.269 (.132)	.138*			
Prescribed an opioid			1.340 (.514)	.195**	
ESAS Physical symptoms	.261 (.107)	.186**	.560 (.121)	.410***	.161*
SF-36 PHC	-.081 (.023)	-.254***			
PCS Total	.032 (.016)	.155*	-.060 (.020)	-.312**	.025**
IES Intrusion	.068 (.022)	.230**			
PASS-20 Cognitive Anxiety			.176 (.040)	.451***	
	$F_{(8,130)} = 12.762, p \leq .0001$, $R^2 = .440$; Adjusted $R^2 = .405$		$F_{(5,98)} = 19.058, p \leq .0001$, $R^2 = .493$; Adjusted $R^2 = .467$		

[a] reference category is ≤ High School; SE b–diff = SE b-difference; KPS, Karnofsky Performance Status Scale; ESAS, Edmonton Symptom Assessment Scale; SF-36 PHC, SF-36 Physical Health Component Score; PCS, Pain Catastrophizing Scale; IES, Impact of Events Scale; PASS-20, Pain Anxiety Symptoms Scale-short form;

* $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

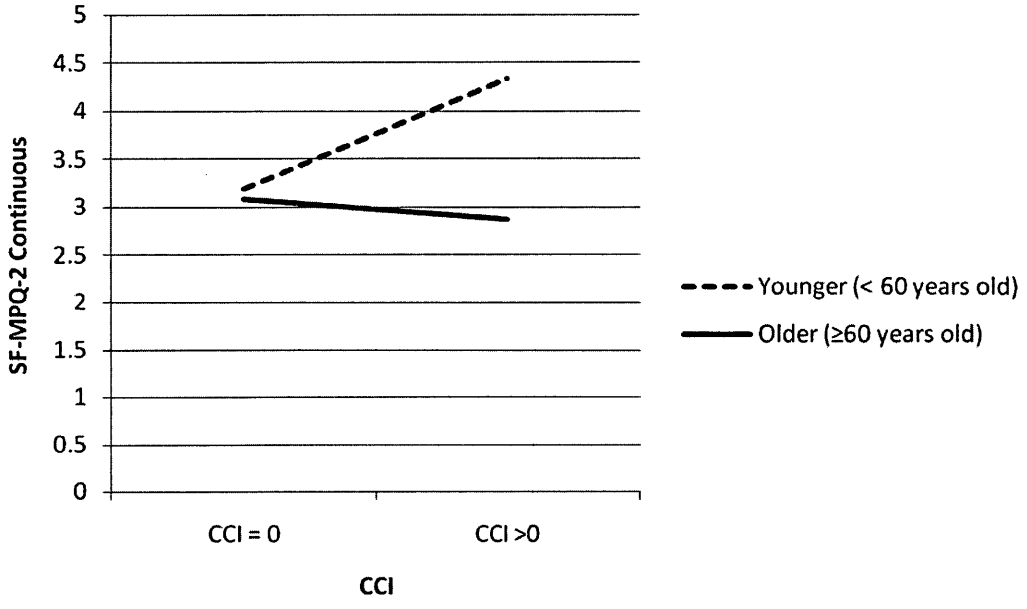

Figure 1. Predicted values of SF-MPQ-2 Continuous pain qualities in two-way interaction between age group and CCI.

Simple slopes analysis revealed the slope for younger patients was significant (B = -1.472 (SE = .462), β = -.338, t = -3.184, p = .002) while the slope for older patients did not reach significance (B = -.107 (SE = .357), β = -.024, t = -.299, p = .78).

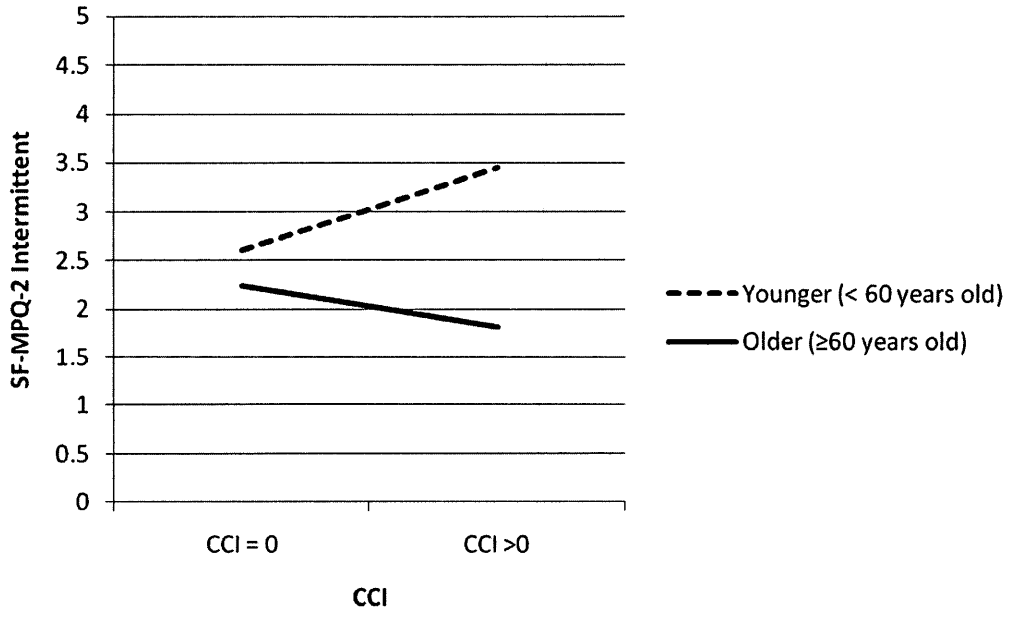

Figure 2. Predicted values of SF-MPQ-2 Intermittent pain qualities in two-way interaction between age group and CCI.

Simple slopes analysis revealed the slope for younger patients was significant (B = -1.637 (SE = .495), $\beta = -.352$, $t = -3.305$, $p = .001$) while the slope for older patients did not reach significance (B = -.365 (SE = .383), $\beta = -.078$, $t = -.953$, $p = .34$).

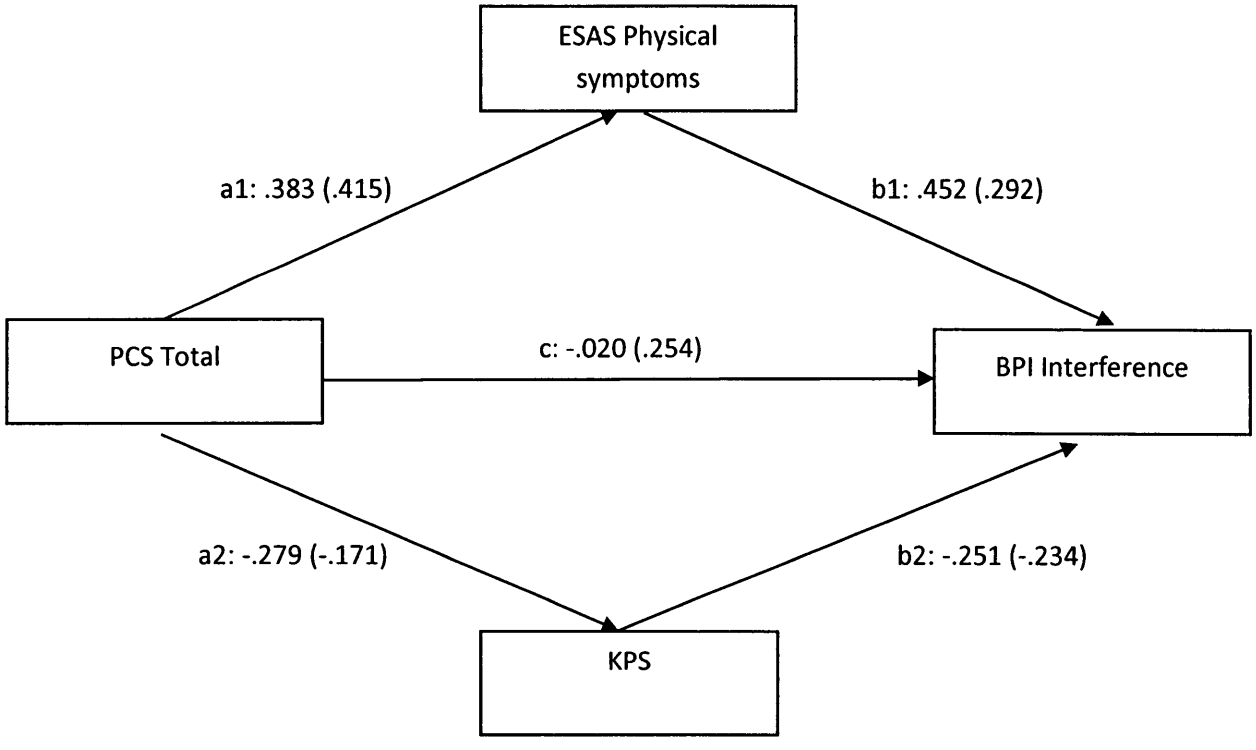

Figure 3. Structural Equation model testing the mediation of ESAS Physical symptoms and KPS on the relationship between PCS Total and BPI Interference.
Unbracketed numbers are Standardized Regression weights from bootstrapped estimates for older patients, bracketed numbers are Standardized Regression weights from bootstrapped estimates for younger patients. Analysis conducted in AMOS (Arbuckle, 1994) Version 20.

BRIDGE FROM CHAPTER 3 TO CHAPTER 4

Data presented in Chapter 3 suggest that in people with cancer pain, there are no age differences in the severity of depressive symptoms. This is consistent with studies of people with cancer pain that have demonstrated that older and younger people may be equally at risk to experience depressive symptoms (Gagliese, Gauthier, & Rodin, 2007; Green & Hart-Johnson, 2010; Kai-hoi Sze, Wong, Lo, & Woo, 2000; Knotkova, Clark, Mokrejs, Padour, & Kuhl, 2004; G. M. Williamson & Schulz, 1995), but it is in contrast to studies of people with cancer that do not consider pain that have shown that older age is associated with less severe depressive symptoms (Compas et al., 1999; Kroenke et al., 2004; Politi, Enright, & Weihs, 2007; Schroevers, Ranchor, & Sanderman, 2004; Vinokur, Threatt, Vinokur-Kaplan, & Satariano, 1990; Wenzel et al., 1999). However, there are no studies that have compared the relationship between age and depressive symptoms in people who do and do not experience cancer pain. Therefore, Chapter 4 presents a preliminary analysis of the relationship between age and depressive symptoms in women who do and do not experience pain three months after breast cancer surgery.

CHAPTER 4

Does Pain Three Months After Breast Cancer Surgery Modify the Relationship Between Depressive Symptoms and Age?

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Introduction

The population is aging (Statistics Canada, 2007). Currently, adults aged 65 and older represent 13% of the population, but this is expected to increase to 25% by the year 2031 (Statistics Canada, 2007) . Although aging is associated with a host of factors, such as increased comorbidities and functional limitations, widowhood, loneliness, and social isolation, which may operate as risk factors for depressive symptoms (VanItallie, 2005), younger age has been associated with greater depressive symptoms (Jorm et al., 2005; Kasen, Cohen, Chen, & Castille, 2003; Klerman & Weissman, 1989; Wickramaratne, Weissman, Leaf, & Holford, 1989). It has been estimated that the prevalence of major depression ranges from 5-10% in the general population, and approximately 5-15% in older people (Barkin, Schwer, & Barkin, 2000; Blazer II & Hybels, 2005; Hasin, Goodwin, Stinson, & Grant, 2005; Reynolds & Kupfer, 1999). A larger proportion of older people may also experience subsyndromal depressive symptoms (Barkin, Schwer, & Barkin, 2000; Blazer II & Hybels, 2005; Lebowitz et al., 1997; Reynolds & Kupfer, 1999; VanItallie, 2005). These seemingly inconsistent findings may be due to cohort effects (Kasen, Cohen, Chen, & Castille, 2003) or the shared etiology of depression and certain diseases (Alexopoulos et al., 1997), which may be more prevalent in older than younger people.

Aging is also associated with the development of cancer (Canadian Cancer Society [CCS], 2013). Depressive symptoms may be prevalent in people with cancer, with 0- 58% of patients experiencing depressive symptoms and 0- 38% meeting criteria for major depression (Massie, 2004). These wide ranges may be due, in part, to different

diagnostic criteria or measurement methodologies and populations studied (Massie, 2004). Consistent with findings from the general population, in people with cancer, greater depression has been associated with younger age (Compas et al., 1999; Kroenke et al., 2004; Politi, Enright, & Weihs, 2007; Schroevers, Ranchor, & Sanderman, 2004; Vinokur, Threatt, Vinokur-Kaplan, & Satariano, 1990; Wenzel et al., 1999). This has led to the suggestion that older people are less psychologically affected by cancer than younger people (Blank & Bellizzi, 2008). One possible explanation for these findings is that among younger people, cancer is perceived as a lifecourse disruption that is inconsistent with normative healthcare expectations or as a threat to the fulfillment of goals, whereas among older people, the process of adapting to other age-related health issues confers a possible protective advantage (Gagliese et al., 2009; Schulz & Heckhausen, 1996; Chapter 3).

However, in people with cancer pain, age is not associated with depressive symptoms (Green & Hart-Johnson, 2010; Kai-hoi Sze, Wong, Lo, & Woo, 2000; Knotkova, Clark, Mokrejs, Padour, & Kuhl, 2004; G. M. Williamson & Schulz, 1995; Chapter 3). This similar to findings from the chronic nonmalignant pain literature where age is not associated with the prevalence or severity of depressive symptoms (Gagliese & Melzack, 1997b; Gagliese & Melzack, 2003; Sorkin, Rudy, Hanlon, Turk, & Stieg, 1990; Turk, Okifuji, & Scharff, 1995). Possible mechanisms for this remain to be elucidated but it may be possible that pain operates as a risk factor for depressive symptoms for both older and younger people which may override the usual age-related protective factors. Studies comparing the relationship between age and depressive symptoms in people with

cancer who do and do not experience cancer pain are not currently available. However, such studies are needed because it may be inappropriate to generalize from the existing literature of people with cancer pain (Green & Hart-Johnson, 2010; Kai-hoi Sze, Wong, Lo, & Woo, 2000; Knotkova, Clark, Mokrejs, Padour, & Kuhl, 2004; G. M. Williamson & Schulz, 1995; Chapter 3) and people without cancer pain (Compas et al., 1999; Kroenke et al., 2004; Politi, Enright, & Weihs, 2007; Schroevers, Ranchor, & Sanderman, 2004; Vinokur, Threatt, Vinokur-Kaplan, & Satariano, 1990; Wenzel et al., 1999) due to cross-study methodological inconsistencies. With the aging population, it is necessary that we improve our understanding of the role of pain in the relationship between age and depressive symptoms in order to design treatments that effectively address the needs of people at different life stages.

In an effort to clarify the relationship between cancer pain and depression, G.M. Williamson and Schulz (1995) evaluated age-related patterns in the mediating role of activity restriction. There were no age differences in pain, depressive symptoms or activity restriction. However, activity restriction fully mediated the relationship between depression and pain in younger, but not older patients (G. M. Williamson & Schulz, 1995). Although the authors suggested that older patients are less distressed by activity restrictions because of lower expectations about functional status and more experience with disability, they did not measure expectations of functioning. Chief among the many methodological limitations present in this study was the use of non-validated measures to assess pain, activity restriction, and comorbidities; therefore, interpretation of this age-related pattern remains problematic.

Breast cancer may represent a particularly suitable setting in which to study these relationships. Older age is associated with the development of breast cancer (Howlader et al., 2013). Surgical excision of the tumor, which often represents initial treatment, has been associated with the development of chronic postoperative pain in 20-60% of women (Jung, Ahrendt, Oaklander, & Dworkin, 2003). More than half of these women may develop neuropathic pain (Haroutiunian, Nikolajsen, Finnerup, & Jensen, 2013). The relationship between chronic breast cancer pain (CBCP) and age has been unclear, with studies demonstrating associations with younger (J. Katz et al., 2005; Poleshuck et al., 2006; W. C. Smith, Bourne, Squair, Phillips, & Chambers, 1999) and older age (Masselin-Dubois et al., 2013; Shimozuma, Ganz, Petersen, & Hirji, 1999; Vinokur, Threatt, Vinokur-Kaplan, & Satariano, 1990), and others reporting no relationship (Carpenter et al., 1998; Kroner, Krebs, Skov, & Jorgensen, 1989). Pain after breast cancer surgery (BCS) is associated with greater depressive symptoms (Miaskowski et al., 2012; Tasmuth, Blomqvist, & Kalso, 1999). Neuropathic pain, defined as pain or sensory symptoms caused by disease or lesions affecting the peripheral and/or central nervous systems (Backonja, 2003), may be particularly distressing; it has been associated with greater pain intensity, interference, and cancer symptomatology and worse mental health quality of life than non-neuropathic cancer pain (Tofthagen & McMillan, 2010). In our study of age-related patterns in cancer pain (Chapter 3), we found that depressive symptoms were associated with greater neuropathic pain to the same extent in both older and younger patients.

There are no studies that have examined the relationship between depressive symptoms and age in women with and without CBCP. The International Association for the Study of Pain suggests that pain that persists for three months or longer may be considered chronic (Merskey & Bogduk, 1994), and it has been suggested that this time point should be used in studies of CBCP in order to facilitate cross-study comparisons (Jung, Ahrendt, Oaklander, & Dworkin, 2003). Since some women experience pain and some do not experience pain three months after BCS, this time point may be ideal to determine whether the presence of pain after BCS impacts on the relationship between depressive symptoms and age. The aim of this preliminary study was to investigate the moderating role of pain three months after BCS on the relationship between depressive symptoms and age. We hypothesized that older age would be associated with fewer depressive symptoms in women who were pain-free three months after BCS, but not in women who experienced pain three months after BCS.

Methods

Participants

Women undergoing unilateral or bilateral lumpectomy or mastectomy at the University Health Network who were recruited between March, 2008 and February, 2013, for a larger, 2-year prospective study of age-related patterns in pain following BCS, were included in this analysis. Exclusion criteria were insufficient English fluency, < 18 years old, American Society of Anesthesiologists class >3, significant CNS, respiratory, cardiac, hepatic, renal or endocrine dysfunction, contraindications to opioids or

acetaminophen, documented Diagnostic and Statistical Manual-IV Axis I disorder or cognitive dysfunction, substance abuse or dependence within one year of the surgery, pregnancy or breastfeeding within 3 months, immunization within 1 month, blood donation within 2 months, and acute infections, illness, allergic reactions, physical injuries or dental work within 2 weeks.

Women were recruited approximately one week prior to surgery during a pre-admission visit at Toronto General Hospital (TGH) or a preoperative patient education session at Princess Margaret Cancer Centre (PMH), University Health Network (UHN). A research assistant (RA) explained the study, and women provided written informed consent to participate. The RA administered the Short Orientation Memory Concentration test (SOMC [Katzman et al., 1983]), collected demographic and health history information, and administered measures of pain and symptom severity during a brief interview at the time of recruitment and by accessing the patient's medical chart. Participants were given a questionnaire package to complete at home and return on the day of surgery. They received a telephone reminder 1-2 days prior to surgery to return their completed questionnaires. On the day of surgery, the RA administered measures of pain, physical and psychological functioning. Clinical and surgical information was collected by accessing patients' medical charts. Three months following surgery (±2 weeks), women were telephoned to complete a follow-up assessment. Women completed the three month follow-up with the RA at UHN if the assessment coincided with a medical appointment; otherwise the assessment was completed via telephone. The RA

first administered the SOMC and then measures of pain, symptom severity, and physical and psychological functioning, then completed the KPS and updated the CCI.

Measures

Cognitive screen. The *Short Orientation-Memory-Concentration Test* (SOMC [Katzman et al., 1983]) is a 6-item measure designed to screen for cognitive impairment and orientation to time, person and place, and memory. It has been validated for use among older adults (Katzman et al., 1983) and has been used in studies of patients with cancer (Rodin et al., 2007).

Measures of Pain. The *Pain History Questionnaire* measures patients' history of painful conditions. It was used to assess patients' experience with chronic nonmalignant pain. Patients were also asked how intense they expected the pain to be immediately after surgery, after medication, and one week following surgery on 11-point Numeric Rating Scales (NRS). An average of these three questions was calculated. The *Short-Form McGill Pain Questionnaire* (SF-MPQ [Melzack, 1987]) is one of the most widely used measures of the multidimensional qualities of pain. It includes 15 items that assess Sensory and Affective pain qualities. Higher scores reflect greater Sensory and Affective pain. It has been validated for use in people with cancer pain (Jensen, 2003b; Ngamkham et al., 2012) and younger and older people with chronic nonmalignant pain (Gagliese & Melzack, 1997a). The *Neuropathic Pain Questionnaire – short form* (SF-NPQ [Backonja & Krause, 2003]) includes 3 items that assess neuropathic pain qualities. It was validated in a large sample of people with diverse pain diagnoses. It differentiates neuropathic from non-neuropathic pain with good sensitivity and specificity (Backonja & Krause, 2003),

and it has been found to differentiate cancer patients with and without neuropathic pain (Mercadante et al., 2009). The *Brief Pain Inventory* (BPI [Cleeland & Ryan, 1994]) includes 4 items that assess the Worst, Least, Average pain intensity in the last 24 hours and Current pain intensity on 11-point NRSs anchored with the words "no pain" and "pain as bad as you can imagine". The Average pain intensity question was used in this analysis. The BPI also includes 7 items that assess interference from pain in general activity, mood, walking ability, work, relations with others, sleep and enjoyment of life with 11-point NRSs anchored with the words "does not interfere" and "completely interferes". A Pain Interference score was calculated from the average of these questions. The BPI has good validity in people with cancer pain (Ger, Ho, Sun, Wang, & Cleeland, 1999; Klepstad, Loge, Borchgrevink, Mendoza, & Cleeland, 2002). *Pain intensity at Rest* (NRS-R) and with *movement* (NRS-M) were assessed with 11-point NRSs anchored with the words "no pain" and "worst possible pain". This response format demonstrates equivalent psychometric properties in younger and older people with pain (Gauthier & Gagliese, 2011). *Satisfaction with pain control* (SAT) was assessed with an 11-point NRS anchored with the words "extremely dissatisfied" and "extremely satisfied".

Analgesic and pharmacologic treatment. The World Health Organization's (WHO) *Analgesic Ladder* was used to categorize prescribed analgesic medication (World Health Organization, 1990). Level 1 consists of non-opioid analgesics (e.g. acetaminophen, nonsteroidal anti-inflammatories) and adjuvant medications (e.g. tricyclic antidepressants, gabapentin) (Bernabei et al., 1998), Level 2 consists of weak opioids (e.g. codeine) and Level 3 consists of strong opioids (morphine). The *Anticholinergic*

Drug Scale (ADS (Carnahan, Lund, Perry, Culp, & Pollock, 2002; Carnahan, Lund, Perry, Pollock, & Culp, 2006) measures the cumulative anticholinergic load of medications. The total score is a sum of all medications based on a potency rating associated with each medication. The ADS has been validated in older people (Carnahan, Lund, Perry, Culp, & Pollock, 2002).

Measures of physical functioning. The *Karnofsky Performance Status Scale* (KPS [Karnofsky & Burchenal, 1949]) measures functional status on a scale ranging from 100 (no evidence of disease) to 0 (death). It was completed by the RA. It has acceptable psychometric properties in people with cancer (Yates, Chalmer, & McKegney, 1980). The *Charlson Comorbidity Index* (CCI [Charlson, Pompei, Ales, & MacKenzie, 1987]) measures the presence of 19 co-occurring conditions. Higher scores indicate greater comorbid load. It is the most recommended comorbidity scale for use in people with cancer (Extermann, 2000a). The RA completed the CCI by reviewing medical charts. The *Edmonton Symptom Assessment Scale* (ESAS [Bruera, Kuehn, Miller, Selmser, & Macmillan, 1991]) measures the intensity of 9 cancer-related symptoms with 11-point NRSs. It has good validity and reliability in people with cancer (Bruera, Kuehn, Miller, Selmser, & Macmillan, 1991). Two factors have been identified. The first factor measures physical symptoms (pain, tiredness, nausea, drowsiness, appetite, wellbeing, shortness of breath) and the second measures psychological symptoms (depression and anxiety) (W. Y. Cheung, Le, & Zimmermann, 2009). The construct validity of the psychological symptom factor has been questioned (Richardson & Jones, 2009; Teunissen, S. C. C. M, de Graeff, Voest, & de Haes, Jun 2007). We therefore used the

average of the physical symptoms (excluding pain) to assess physical symptom severity. The *SF-12* (J. Ware Jr., Kosinski, & Keller, 1996) is a brief, 12-item measure of physical and mental health QOL. It has good psychometric properties in people with cancer (Thome & Hallberg, 2004).

Measures of psychological functioning. The *Pain Catastrophizing Scale* (PCS [Sullivan, Bishop, & Pivik, 1995]) measures ruminative thoughts about pain, magnification of the negative implications of pain, and helpless attitudes toward pain management. Higher scores reflect greater catastrophizing about pain. It has good psychometric properties in people with chronic nonmalignant pain and has been used in women with postoperative pain from BCS (Schreiber et al., 2013). The *Pain Anxiety Symptoms Scale* (PASS [McCracken & Gross, 1995]) is a 40-item measure fear of pain, physiological anxiety, escape and avoidant thoughts, and cognitive anxiety. Higher scores reflect greater pain-related anxiety. It has good validity and reliability (Coons, Hadjistavropoulos, & Asmundson, 2004; Roelofs et al., 2004). The *Center for Epidemiologic Studies – Depression Scale* (CES-D [Radloff, 1977]) includes 20-items that assess the frequency of depressive symptoms over the past week. Higher scores reflect greater depressive symptoms. It has been used extensively and has excellent validity and reliability (Beeber, Shea, & McCorkle, 1998; Coyle & Roberge, 1992; Gauthier & Gagliese, 2011; Pasacreta, 1997). The *State-Trait Anxiety Inventory* (STAI) includes 20-items that measure dispositional (Trait) anxiety and 20-items that measure situation-specific anxiety (State) (Spielberger, 1977). Higher scores reflect greater state

or trait anxiety. It has excellent psychometric properties in diverse patient populations (Julian, 2011) including postoperative patients (Granot & Ferber, 2005).

Data Analysis

Less than 1% of the sample who completed the three month assessment left one or more items missing on one or more measures at this follow-up. Age, and depressive symptoms and pain at three months were not associated with missing data (all $p \geq .07$). As this was a preliminary study, we computed scores for women with complete data. Descriptive statistics were used to characterize the sample. Bivariate tests of association were conducted with Pearson and Spearman's correlations. Fisher's Z-transformations compared the strength of correlations between age and depression in those with and without pain. Interaction models were fit in order to identify the moderating role of pain at three months on the relationship between age and depression. Age was grand-mean centered and product terms were calculated with three month pain variables. A stepwise order of entry was used with the product term entered in the second step (Aiken & West, 1991; Holmbeck, 2002). Interactions were investigated graphically by plotting the simple slopes of age by pain status at three months (Holmbeck, 2002).

Results

Participant Characteristics

Figure 1 displays the patient flow diagram. Between March, 2008 and February, 2013, 377 women were approached. One hundred and ninety-three women (51.2%) refused to participate. Reasons for refusal included lack of interest (n=66; 34.2%), lack of

time (n = 40; 20.7%), being upset or overwhelmed just prior to surgery (n = 22; 11.4%), participation in a conflicting study (n = 13; 6.7%) and living too far from the hospital to complete follow-ups (n = 2; 1.0%). An additional 44 women (22.8%) gave no reason for refusing to participate. One hundred and eighty-four women (48.8%) agreed to participate. After giving informed consent to participate, 9 (4.9%) voluntarily withdrew their participation and 5 (2.7%) were excluded because of changes to the date or location of surgery. One hundred and seventy women (92.4%) completed the preoperative and OR day assessments. Seven (3.8%) subsequently withdrew their participation and 8 (4.3%) were excluded. We were unable to contact 31 (16.8%) for the three month follow-up. One hundred and twenty-four women (67.4%) completed the three month assessment and comprise the sample for this analysis.

Demographics

Women who completed the three month follow-up were compared to women who withdrew or who were excluded (n=29) and women who were lost to follow-up (n=31) on demographic, clinical, and surgical factors. There were no differences between the groups (all $p \geq .07$).

Demographic, clinical, surgical, and preoperative and three month pain, physical and psychological characteristics of women who completed the three month assessment are presented in Table 2. Women were 52.00 ± 11.39 years old. Procedure was evenly split: 55.6% underwent mastectomy and 44.4% underwent lumpectomy. Although 25% reported a history of chronic pain, preoperative pain intensity was low: The median on all preoperative and OR day measures of pain intensity was 0.

Preoperatively, 23 (19.0%) had BPI Average pain intensity ≥3/10, or moderate-to-severe pain intensity (MSPI [L. O. Andersen et al., 2009; Jensen, Smith, Ehde, & Robinsin, 2001; Masselin-Dubois et al., 2013; Schreiber et al., 2013]), and 7 (5.6%) scored ≥ cutoff on the SF-NPQ, scores which may indicate the presence of neuropathic pain (NeP [Backonja & Krause, 2003; Mercadante et al., 2009]). Forty-five women scored ≥16 on the CES-D, scores with may indicate the presence of clinically relevant depressive symptoms (Radloff, 1977).

At the three month follow-up, 25 women (20.2%) had MSPI and 19 (15.3%) had NeP. At this follow-up, 24 women (19.4%) scored ≥16 on the CES-D.

Hypothesis Testing

In order to test the hypothesis that the presence of pain three months after BCS moderates the relationship between age and depressive symptoms, BPI Average pain intensity, BPI Pain Interference, SF-NPQ and SF-MPQ Sensory and Affective subscales data were dichotomized as follows:

1) BPI Average pain intensity = 0/10 vs. >0/10;

2) BPI Average pain intensity <3/10 vs. ≥3/10 (MSPI);

3) BPI Average Pain Interference = 0/10 vs. >0/10;

4) BPI Average Pain Interference <3/10 vs. ≥3/10;

5) SF-NPQ below cutoff vs. at or above SF-NPQ cutoff (NeP);

6) SF-MPQ Sensory = 0/33 vs. >0/33;

7) SF-MPQ Affective =0/12 vs. ≥0/12.

These cut-offs were selected based on inspection of the raw data and studies identifying cutoffs for moderate-to-severe average pain intensity in women with breast cancer (Masselin-Dubois et al., 2013; Schreiber et al., 2013) . These pain groups were used in subsequent analyses.

Age was negatively correlated with preoperative CES-D (r = -.23, p = .01) and three month CES-D (r = -.24, p = .008). Table 3 presents correlations between pain groups, age, and CES-D at three months. Age was not correlated with pain groups (all $p \geq$ .14). Pain at three months was correlated with three-month CES-D (all $r \geq .31$) but not preoperative CES-D (all $r \leq .16$).

The strength of the bivariate correlations between age and CES-D were compared across pain groups with Fisher's Z-tests (Table 4). The correlation between age and CES-D was significantly stronger in women without MSPI than women with MSPI (p = .05). In women without MSPI, age was negatively correlated with depressive symptoms (r = -.29, p =.004), but in women with MSPI, age and CES-D were not correlated (r = -.01, p = .95). In this pain group, although the interaction was nonsignificant (B = .19 (SE = .21), β = .19, t = -.88, p = .38), inspection of the slopes revealed that, consistent with our hypothesis, in women without MSPI, depression was associated with younger age, while in women with MSPI, depression was not associated with age (Figure 2).

There was a significant interaction between age and three month SF-NPQ in relation to 3-month CES-D scores (B = -.63 (SE = .24), β = -.66, t = -2.65, p = .009). Counter to our hypothesis, in women with NeP, depression was associated with younger

age. However, in women without NeP, depression and age were not associated (Figure 3). There were no other significant interactions based on pain group (all $p \geq .5$)

We also tested the moderating role of preoperative pain on the relationship between age and three month CES-D using the same pain groupings described above for preoperative pain measures. None of the interactions were significant (all $p \geq .5$), suggesting that pain three months after BCS, but not preoperative pain, moderates the relationship between age and depressive symptoms.

We explored demographic, clinical, surgical, and preoperative and three-month pain interference and qualities, and physical, and psychological differences between older and younger women with and without (1) MSPI and (2) NeP at 3 months, in separate analyses. Due to the distribution of the data, age groups were defined based on the 25th and 75th percentile (Field, 2009; McCluskey & Lalkhen, 2007; Tabachnick & Fidell, 2012). Although this likely resulted in decreased power to detect a difference, this analysis simply represents a preliminary exploration of differences between the youngest and oldest women with and without pain and provides an idea about the variability of the data across groups. Thirty-four women aged 59-81 comprised the older group and thirty-four women aged 27-44 comprised the younger group. Analyses were conducted using χ^2 tests with Yates' correction for small cell sizes, one-way ANOVAs, and Kruskal-Wallice nonparametric tests. A Bonferroni correction was applied to the omnibus tests of significance to control for multiple comparisons (adjusted $\alpha = .05/50 = .001$). Planned pairwise comparisons of nonparametric data between younger and older women with

pain (either MSPI or NeP) and younger and older pain-free women were conducted with Mann-Whitney U tests with a Bonferroni corrected alpha (adjusted $\alpha = .05/2 = .025$).

To test (1) age group differences in women with and without MSPI at 3 months, four groups were formed. There were twenty-four (70.6%) younger women without MSPI (Y-noMSPI), 10 (29.4%) younger women with MSPI (Y-MSPI), 29 (85.3%) older women without MSPI (O-noMSPI) and 5 (14.7%) older women with MSPI (O-MSPI).

Preoperative expectations of pain after surgery differed across age and pain groups ($F(3,64) = 6.95, p < .001$). Post-hoc pairwise comparisons revealed that Y-MSPI and Y-noMSPI had higher expectations of pain after surgery than O-noMSPI ($p \leq .008$; Figure 4).

Three month ESAS Physical symptom severity differed across age and pain groups ($F(3,64) = 7.58, p < .001$). Post-hoc pairwise comparisons revealed that Y-MSPI had greater ESAS symptom severity than Y-noMSPI and O-noMSPI ($p \leq .01$; Figure 5).

Three month STAI-S total also differed across age and pain groups ($F(3,64) = 6.50, p < .001$). Post-hoc pairwise comparisons revealed that Y-MSPI had greater STAI-S total scores than Y-noMSPI and O-noMSPI ($p \leq .02$; Figure 6).

The Kruskal-Wallice omnibus tests of group differences in three-month SF-MPQ Sensory, SF-MPQ Affective, and BPI Interference scores were significant (all $p \leq .001$) but planned pairwise comparisons of Y-MSPI vs. O-MSPI and Y-noMSPI vs. O-noMSPI were nonsignficant (all $p \geq .10$)

To test (2) age group differences based on three-month NeP, four groups were formed. There were 30 (88.2%) younger women without NeP (Y-noNeP), 4 (11.8%)

younger women with NeP (Y-NeP), 31 (91.2%) older women without NeP (O-noNeP), and 3 (8.8%) older women with NeP (O-NeP). The only factor that differed across groups was preoperative expectations of pain after surgery ($F(3,64) = 7.219, p < .001$). Post-hoc tests revealed that Y-NeP and Y-noNeP had higher expectations of pain after surgery than O-noNeP ($p \leq .01$; Figure 7). There were no differences between O-NeP and the rest of the groups (all $p > .51$).

Discussion

In this preliminary investigation of the relationship between depressive symptoms and age in women with and without pain three months after BCS, 20% of the women experienced moderate-to-severe pain intensity and 15% experienced neuropathic pain at three months. Age was not associated with pain at three months. Three further noteworthy findings are evident. First, we found partial support for our hypothesis that pain three months after BCS moderates the relationship between depressive symptoms and age. Specifically, in women with moderate-to-severe pain intensity, depressive symptoms and age were not associated, but in women with mild or no pain, depressive symptoms were associated with younger age. However, in contrast, depressive symptoms were associated with younger age only in women with neuropathic pain, but not in women without neuropathic pain. Second, the physical and psychological impact of having moderate-to-severe pain intensity was not age related: Older and younger women with pain intensity within this range did not differ in the severity of other cancer symptoms or state anxiety. Third, high preoperative pain expectations were associated with moderate-to-severe pain intensity and neuropathic pain at three months in both older

and younger women. These preliminary data provide important directions for future research, including the need to address excessively high preoperative pain expectations among older and younger women.

This is the first study to demonstrate that pain moderates the relationship between age and depression in a sample of people with and without cancer-related pain. Specifically, in women with moderate-to-severe pain intensity three months after BCS, age was not associated with depressive symptoms, but in women mild or no pain, younger age was associated with higher depressive symptoms. These findings are consistent with studies of people with cancer pain that have shown that age is not related to depressive symptoms (Green & Hart-Johnson, 2010; Kai-hoi Sze, Wong, Lo, & Woo, 2000; Knotkova, Clark, Mokrejs, Padour, & Kuhl, 2004; G. M. Williamson & Schulz, 1995; Chapter 3), and with studies that do not consider pain that have shown that younger age is associated with greater depressive symptoms (Compas et al., 1999; Kroenke et al., 2004; Politi, Enright, & Weihs, 2007; Schroevers, Ranchor, & Sanderman, 2004; Vinokur, Threatt, Vinokur-Kaplan, & Satariano, 1990; Wenzel et al., 1999).

Intriguingly, the reverse was true with respect to neuropathic pain. In women with neuropathic pain, younger age was associated with higher depressive symptoms, whereas in women without neuropathic pain, age was not associated with depressive symptoms. Thus, there is some evidence to support the idea that cancer pain may override protective factors that may be present in older people (Gagliese, Gauthier, & Rodin, 2007) but this may not be true in the context of neuropathic pain. Mechanisms underlying these differences are beyond the scope of this preliminary study and remain to be elucidated.

Neuropathic pain has been associated with greater pain intensity, interference, and cancer symptom severity, and worse mental health quality of life than non-neuropathic pain (Mercadante et al., 2009; Tofthagen & McMillan, 2010). It may also be refractory to treatment (Dworkin et al., in press; Mercadante & Portenoy, 2001). In the general population, age differences in the correlates of depression have been reported (Regan, Kearney, Savva, Cronin, & Kenny, 2013). The presence of chronic nonmalignant pain was a common correlate of depression in both older and middle-aged people. Neuropathic pain was not measured. It might be possible that the present finding reflects an age-related pattern in a correlate of depressive symptoms in women with breast cancer, however, this requires replication, therefore remains highly speculative.

Pain-related interference did not moderate the relationship between age and depressive symptoms. However, in a previous study of cancer patients, an age-related pattern in the role of activity restriction in the relationship between pain and depression was reported (G. M. Williamson & Schulz, 1995). Specifically, G.M. Williamson and Schulz (1995) found that activity restriction fully mediated the relationship in younger patients, but only partially mediated the relationship in older patients. This is consistent with a previous study of people with chronic nonmalignant pain, where pain interference and life control mediated the relationship between pain and depression for younger, but not older people (Turk, Okifuji, & Scharff, 1995). Several issues prevent the integration of the findings from the present study with those of G.M. Williamson and Schulz (1995). Primarily, age-related equivalence in the validity and reliability of the measures used in that study is unknown. It is therefore difficult to know whether the age-related patterns in

activity restriction model are due to actual age-related patterns, or differences in the way the measures operated in each age group. Furthermore, it is unclear if their measure of activity restriction is specific to cancer, pain, or more general activity. They did not test the role of pain in the relationship between age and depressive symptoms.

Based on their findings, G.M. Williamson and Schulz (1995) suggested that older people have lower expectations of functional ability and are therefore less distressed by activity restriction than younger people; however, they did not measure this. Studies comparing expectations of functioning and their relationship to depressive symptoms in older and younger people with cancer pain are not available. Outside of the context of cancer, only 13% to 20% of older people have attributed functional limitations to aging, and depressive symptoms did not differ between those who held this attribution and those who did not (Sarkisian, Liu, Ensrud, Stone, & Mangione, 2001; J. D. Williamson & Fried, 1996). Interestingly, older people with chronic nonmalignant pain were not more likely than younger people to attribute pain to aging (Gagliese & Melzack, 1997b). Other potentially important factors which have not been considered but which may account for the age-related pattern in the activity restriction model may be retention or replacement of important activities or activity modification (Duke, Leventhal, Brownlee, & Leventhal, 2002; Gagliese et al., 2009; P. A. Parmelee, Harralson, Smith, & Schumacher, 2007). Taken together with the existing literature demonstrating no age differences in depressive symptoms in people with cancer pain (Green & Hart-Johnson, 2010; Kai-hoi Sze, Wong, Lo, & Woo, 2000; Knotkova, Clark, Mokrejs, Padour, & Kuhl, 2004; G. M. Williamson & Schulz, 1995; Chapter 3), these converging lines of evidence do not support the

activity restriction model but instead support the hypothesis that the presence of pain equalizes the risk for depressive symptoms in younger and older people with cancer. If this is true, unresolved, intense pain may represent an especially critical risk factor for depression among older women after BCS. However, because this is a preliminary study, more research is needed to compare the two models before drawing firm conclusions.

The relationship between pain intensity and interference may be nonlinear (Paul, Zelman, Smith, & Miaskowski, 2005; Serlin et al., 1995). Mild pain (pain intensity of ≤4/10 on an NRS) has been associated with minimal pain interference, whereas moderate-to-severe pain (>4/10) has been associated with much greater levels of pain interference and compromised QOL (Paul et al., 2005; Serlin et al., 1995).These "cutpoints" were established in heterogeneous samples of cancer patients at different disease stages. It has also been shown that cutpoints may vary across patient populations (Jensen et al., 2001). The identification of cutpoints has clinical relevance because it may be possible for healthcare providers to make treatment decisions based on patients' reports of pain intensity that improve functioning and QOL (Jensen et al., 2001). In the present analysis, the relationship between age and depressive symptoms was not moderated by pain using a cutpoint of >0/10 on an NRS of average pain intensity, but there was an effect when a cutpoint of ≥3/10, moderate-to-severe pain, was used. Women reporting this level of average pain intensity had much higher depressive symptoms than women reporting less intense pain, regardless of age. Although there is no established cutpoint for clinically significant pain after BCS that is consistently used across studies, two recent studies using this cutpoint have demonstrated that women who experience

greater pain intensity report worse psychological wellbeing than women with less intense pain (Masselin-Dubois et al., 2013; Schreiber et al., 2013). Taken together with the present study, it may be possible that this cutpoint has clinical relevance for women three months after BCS, however future research is needed to validate cutpoints for clinically significant pain in this population.

Consistent with the findings in Chapter 3, we did not find support for the suggestion that older people are less psychologically affected by cancer than younger people (Blank & Bellizzi, 2008), in the context of cancer pain. Although these analyses were exploratory, it appears that the impact of moderate-to-severe pain intensity three months after BCS is not age-related. Pain qualities, pain interference, severity of other cancer symptoms and state anxiety appear to be just as bad for older and younger women with pain after BCS. Chronic pain after BCS has been associated with impaired physical functioning, increased anxiety and pain catastrophizing, and reduced quality of life (Carpenter et al., 1998; Deimling, Sterns, Bowman, & Kahana, 2005; Macdonald, Bruce, Scott, Smith, & Chambers, 2005; Schreiber et al., 2013). However, these findings are derived from retrospective analyses and studies comparing the impact of chronic pain after BCS in older and younger women are not available. This is the first study to consider the potential for age-related patterns in the impact of pain three months after BCS using a prospective design, but studies with larger sample sizes are required.

Whereas a number of biomedical and psychological pre- and postoperative risk factors for the development of pain after BCS have been identified (K. G. Andersen & Kehlet, 2011), this is the first study to identify preoperative pain expectations as a

predictor of moderate-to-severe pain intensity and neuropathic pain three months after BCS. Having lower preoperative expectations of pain seemed to operate as a protective factor for the development of pain, particularly for older women. Higher preoperative pain expectations have also been associated with greater acute postoperative pain in women with breast cancer (Montgomery, Schnur, Erblich, Diefenbach, & Bovbjerg, 2010) and greater postoperative pain in other patient populations (Wallace, 1985). Interestingly, older age has been associated with lower preoperative pain expectations (Gagliese, Jackson, Ritvo, Wowk, & Katz, 2000; Schnur et al., 2007) and fewer expected side effects of cancer treatment (Hofman et al., 2004). Other predictors of preoperative pain expectations have included preoperative distress, trait anxiety, and family history of cancer (Schnur et al., 2007). While preliminary, the present findings may have implications for preoperative clinical care, specifically the development of preoperative interventions that address pain expectations.

The novelty of this study lies in its prospective design and identification of pain outcome-specific relationships between age and depressive symptoms. The design of this study improves on prior studies of pain after BCS which have been retrospective, with assessments occurring years or decades after surgery (Macdonald, Bruce, Scott, Smith, & Chambers, 2005; Reyes-Gibby, Morrow, Bennett, Jensen, & Shete, 2010; Schreiber et al., 2013). Additionally, we included women who reported preoperative pain. This is important, as it provides a representative clinical picture of women undergoing BCS and enhances the external validity of our findings. Despite these strengths, there are several limitations that must be considered. The limited sample size and preliminary nature of

this study must be taken into account when interpreting the findings. Additionally, although the measure of neuropathic pain used in this study was validated in a large sample of people with diverse range of painful conditions (Backonja & Krause, 2003) and it has been found to differentiate cancer patients with and without neuropathic pain (Mercadante et al., 2009), it requires validation in younger and older women with breast cancer. Until it has been validated in this population and age-related factorial invariance has been established, age-related patterns detected with this scale must be interpreted with caution.

Some important future directions that derive from these results involve determining the trajectory of non-neuropathic and neuropathic pain and depression in older and younger women as well as age-related predictors of the development of pain three months after BCS with a larger sample size. It will also be important to replicate these findings in people with other cancers. Moreover, given the potential importance of preoperative pain expectations to long-term postoperative pain outcomes for older and younger women, much more research into the predictors of preoperative pain expectations is needed, including possible age-related predictors. Related, early research has established that preoperative patient preparation, including providing information about the procedure, as well as pain and other side effects after the procedure, impacts on postoperative outcomes (Egbert, Battit, Welch, & Bartlett, 1994; Suls & Wan, 1989). Future research investigating preoperative educational interventions that address pain expectations for women undergoing BCS is required.

In summary, these findings suggest that having moderate-to-severe pain intensity three months after BCS cancels out whatever protective factors exist against depressive symptoms in older people without pain. However, the reverse may be true in women with NeP; younger women with NeP may be at particular risk for depressive symptoms. One potentially mitigating factor for the development of chronic postsurgical pain may be lower preoperative pain expectations. While this study requires replication with a larger sample size in order to draw definitive conclusions, it provides early but important information about the role of pain due to BCS in the relationship between depressive symptoms and age. Although most women may be pain-free prior to surgery, a significant minority of women may develop chronic pain due to BCS, independent of age. With the aging population (Statistics Canada, 2007), and the greater risk for breast cancer with increasing age (Howlader et al., 2013), the proportion of older women who may require treatment for cancer-related pain and depression will grow. A better understanding of depression and pain across the adult life span is necessary in order to provide treatment that properly addresses the needs of people at different life stages.

Table 1. Measures at each assessment included in this analysis

	Preadmission	OR-day	3 months postop
Pain			
Pain history	X		
SF-MPQ	X	X	X
SF-NPQ	X	X	X
BPI	X		X
NRS-R	X	X	
NRS-M	X	X	
SAT			X
Analgesic treatment			
WHO Analgesic Ladder	X		X
ADS	X		
Physical Functioning			
KPS	X		X
CCI	X		X
ESAS	X	X	X
SF-12 PHC	X		X
Menstrual status	X		X
Psychological Functioning			
Pain expectations	X		
PCS	X		
PASS	X		
CES-D	X		X
STAI-S	X	X	X
STAI-T	X		
SF-12 MHC	X		X

Notes. SF-MPQ, Short-form McGill Pain Questionnaire; SF-NPQ, Neuropathic Pain Questionnaire short-form; BPI, Brief Pain Inventory; NRS-R and M, Numeric Rating Scale Rest and Movement; SAT, Satisfaction with Pain Control; WHO, World Health Organization; ADS, Anticholinergic Drug Scale; KPS, Karnofsky Performance Status

scale; CCI, Charlson Comorbiditiy Index; ESAS, Edmonton Symptom Assessment Scale; SF-12 PHC, SF-12 Physical Health Component Score; PCS, Pain Catastrophizing Scale; PASS, Pain Anxiety Symptom Scale; CES-D, Center for Epidemiologic-Studies Depression scale; STAI-S, State Trait Anxiety Index – State; STAI-T, State Trait Anxiety-Trait; SF-12 MHC, SF-12 Mental Health Component Score.

Table 2. Descriptive statistics and preoperative pain, physical and psychological factors (n=124)

	Mean ± SD; n (%)
Age	52.00 ± 11.39 (range 27-81)
Caucasian ethnicity	106 (85.5)
Marital status	
Married/partnered	92 (74.2)
Single	13 (10.5)
Separated/Divorced	12 (9.7)
Widowed	7 (5.6)
Missing	1 (.8)
BMI	26.63 ± 5.58
Menopausal	73 (58.9)
Previous surgeries for breast cancer	55 (44.4)
History of chronic nonmalignant pain	31 (25)
Procedure	
Lumpectomy	55 (44.4)
Mastectomy	69 (55.6)
Laterality	
Right	43 (34.7)
Left	45 (36.3)
Bilateral	36 (29.0)
Stage (American Cancer Society Staging)	
Stage 0	8 (6.5)
Stage 1	34 (27.4)
Stage 2	20 (16.1)
Stage 3	12 (9.7)
Prophylactic	30 (24.2)
Missing	20 (16.1)

Axillary node dissection	24 (19.4)
Missing	25 (20.2)
Sentinel node biopsy	60 (48.4)
Missing	24 (19.4)
Preoperative pain, treatment, physical and psychological factors	
ADS (median, IQR)	0 (0, 0)
WHO Analgesic Ladder	
None	87 (70.2)
Level 1	26 (21)
Level 2	2 (1.6)
Missing	9 (7.3)
CCI >0	4 (3.2)
KPS	90.85 ± 9.92
ESAS Physical symptom severity	1.52 ± 1.17
SF-12 PHC	52.93 ± 8.83
NRS-R (median, IQR)	0 (0, .5)
NRS-M (median, IQR)	0 (0, 2)
SF-MPQ Sensory (median, IQR)	0 (0, 1)
SF-MPQ Affective (median, IQR)	0 (0, 0)
BPI Interference (median, IQR)	0 (0, 1.25)
SF-NPQ ≥ cutoff	7 (5.6)
Pain expectations	3.39 ± 1.90
PCS Rumination	9.99 ± 4.10
PCS Magnification	5.81 ± 2.41
PCS Helplessness	11.32 ± 4.70
PCS Total	26.91 ± 10.51
PASS Fear	8.64 ± 6.65
PASS Escape-Avoidance	20.09 ± 7.78
PASS Physiological Anxiety	12.00 ± 8.88

PASS Cognitive Anxiety	18.76 ± 9.07
PASS Total	59.50 ± 28.74
CES-D	14.55 ± 10.54
STAI-S	41.66 ± 12.32
STAI-T	36.01 ± 11.66
SF-12 MHC	45.23 ± 16.02
OR Day	
NRS-R (median, IQR)	0 (0, 1)
NRS-M (median, IQR)	0 (0, 1)
SF-MPQ Sensory (median, IQR)	0 (0, 1)
SF-MPQ Affective (median, IQR)	0 (0, 0)
SF-NPQ ≥ cutoff	3 (2.5%)
3 Month	
SF-MPQ Sensory: median (IQR)	0 (0,2)
SF-MPQ Affective: median (IQR)	0 (0,0)
BPI Interference: median (IQR)	.07 (0-1.34)
Satisfaction with pain control	8.87 ± 2.25
KPS	91.19 ± 6.01
Wound healing problems*	3 (2.4)
ESAS Physical symptom severity	1.44 ± 1.23
SF-12 PHC	45.46 ± 9.48
CES-D	8.96 ± 8.21
STAI-S	30.03 ± 10.67
SF-12 MHC	53.65 ± 9.61

* includes necrosis, epidermolysis, and/or infection

Note. BMI, body mass index; ADS, Anticholinergic Drug Scale; WHO, World Health Organization; CCI, Charlson Comorbidity Index; KPS, Karnofsky Performance Status Scale; ESAS, Edmonton Symptom Assessment Scale; PHC, SF-12 Physical Health Component Score; NRS, Numeric Rating Scale; SF-MPQ, Short-Form McGill Pain

Questionnaire; BPI, Brief Pain Inventory; SF-NPQ, Neuropathic Pain Questionnaire-short-form; PCS, Pain Catastrophizing Scale; PASS, Pain Anxiety Symptom Scale; CES-D, Center for Epidemiologic Studies-Depression scale; STAI-S, State Trait Anxiety Inventory-State; STAI-T, State-Trait Anxiety Inventory-Trait; MHC, SF-12 Mental Health Component Score.

Table 3. Correlations between age, pain at three months, and depressive symptoms at three months and preoperatively

	Age (years)	3 month CES-D	Preoperative CES-D
BPI Average pain intensity >0/10	-.12	.45**	.16
BPI Average pain intensity ≥3/10	-.13	.35**	.15
BPI Interference >0/10	-.06	.36**	.14
BPI Interference ≥3/10	-.09	.39**	.06
SF-NPQ	-.07	.35**	.04
SF-MPQ Sensory > 0	.003	.31**	.01
SF-MPQ Affective > 0	-.03	.43**	.04

**$p \leq 0.01$.

Values are Spearman's rho

Note. BPI, Brief Pain Inventory; SF-NPQ, Neuropathic Pain Questionnaire short-form; SF-MPQ, Short-Form McGill Pain Questionnaire; CES-D, Center for Epidemiologic Studies – Depression Scale.

Table 4. Correlations between age and three month CES-D by pain three months after breast cancer surgery

		*P**
BPI Average pain intensity = 0/10; n=62 (50%) r = -.31, p = .01	**BPI Average pain intensity >0/10; n = 62 (50%)** r = -.13, p = .30	.30
BPI Average pain intensity <3/10; n=99 (79.8%) r = -.29, p = .01	**BPI Average pain intensity ≥3/10; n = 25 (20.2%)** r = -.01, p = .95	.05
SF-MPQ Sensory = 0/33; n=64 (51.6%) r = -.28, p = .03	**SF-MPQ Sensory >0/33; n = 60 (48.4%)** r = -.24, p = .07	.81
SF-MPQ Affective = 0/12; n = 99 (79.8%) r = -.28, p = .005	**SF-MPQ Affective >0/12; n = 24 (19.4%)** r = -.16, p = .44	.60
SF-NPQ below; n = 105 (84.7%) r = -.15, p = .13	**SF-NPQ ≥ cutoff; n = 19 (15.3%)** r = -.57, p = .01	.07
BPI Interference = 0/10; n = 62 (50.5%) r = -.25, p = .05	**BPI Interference >0/10; n = 62 (50.0%)** r = -.21, p = .11	.81
BPI Interference <3/10; n = 109 (87.9%) r = -.24, p = .01	**BPI Interference ≥3/10; n = 15 (12.1%)** r = -.21, p = .44	.87

*P value for Fisher's Z test comparing the strength of correlations between the groups.

Note. BPI, Brief Pain Inventory; SF-MPQ, Short-Form McGill Pain Questionnaire; SF-NPQ, Neuropathic Pain Questionnaire short-form; CES-D, Center for Epidemiologic Studies – Depression Scale.

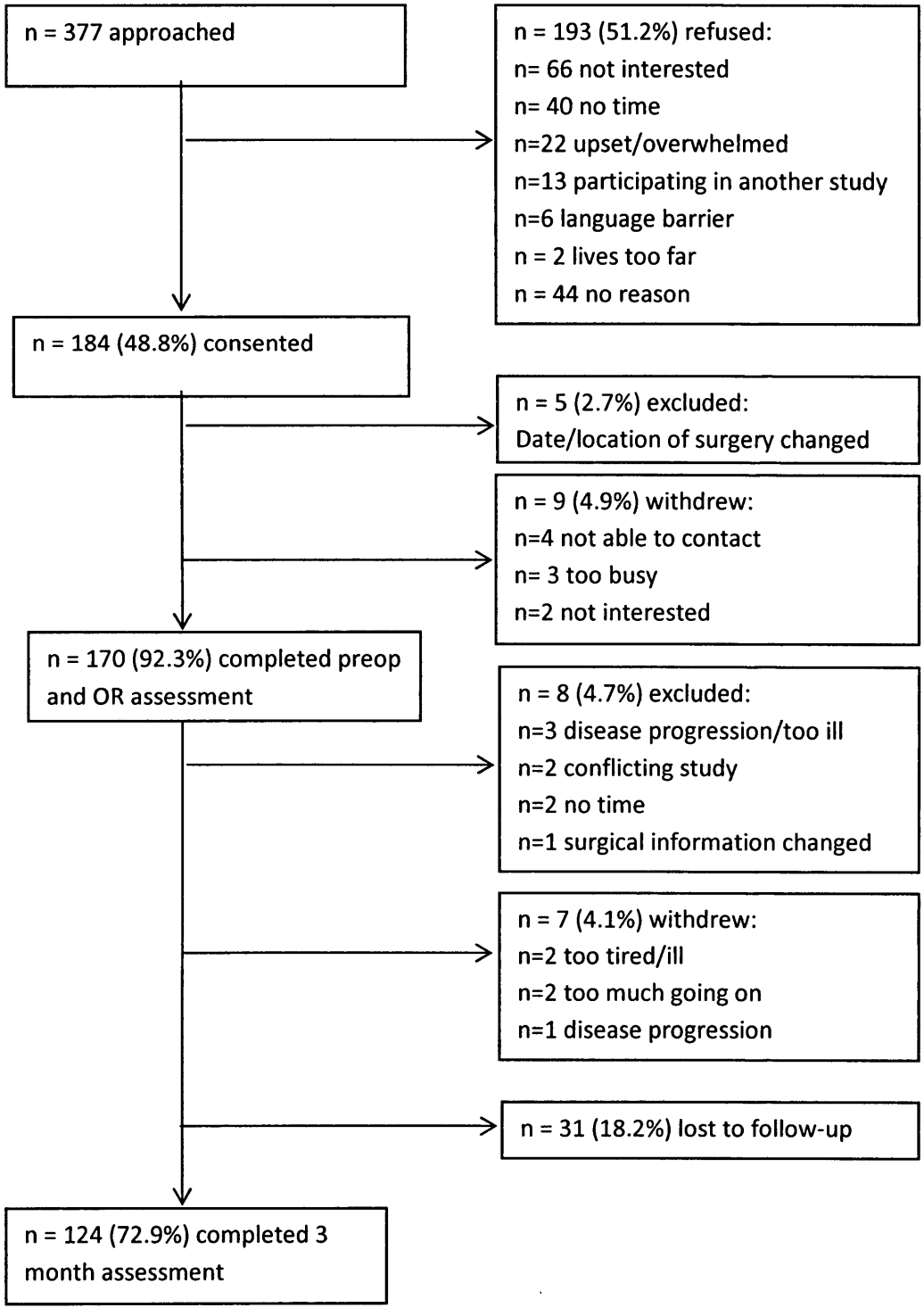

Figure 1. Patient flow diagram

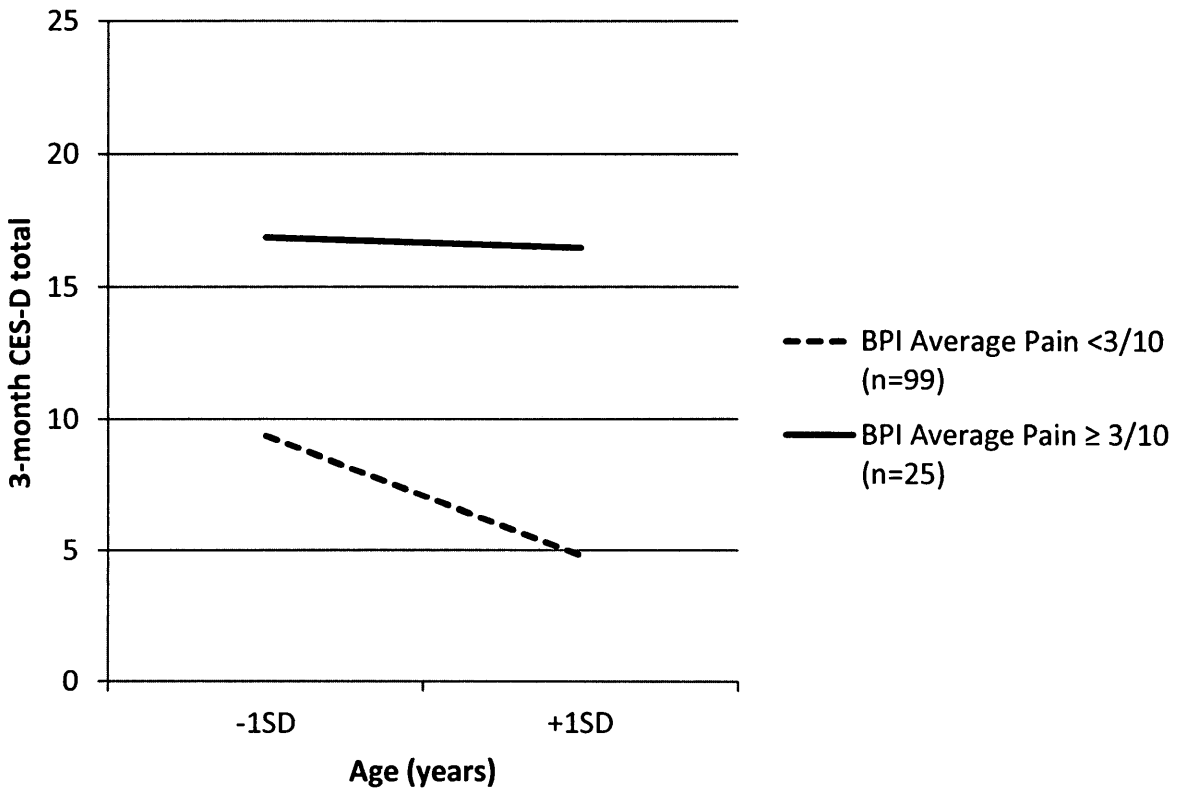

Figure 2: Interaction between age and three month BPI Average pain intensity in relation to three month CES-D total scores.

Simple slopes analysis revealed the slope for women mild or no pain (BPI Average Pain <3/10) three months after breast cancer surgery was significant (B= -.20 (SE = .08), β = -.23, t = -2.50, p = .01) while the slope for women with moderate-to-severe pain intensity (BPI Average Pain ≥3/10) was nonsignificant (B = -.02 (SE = .20), β = -.02, t = -.09, p = .93).

Notes. BPI, Brief Pain Inventory; CES-D, Center for Epidemiologic Studies Depression scale; SD, Standard Deviation

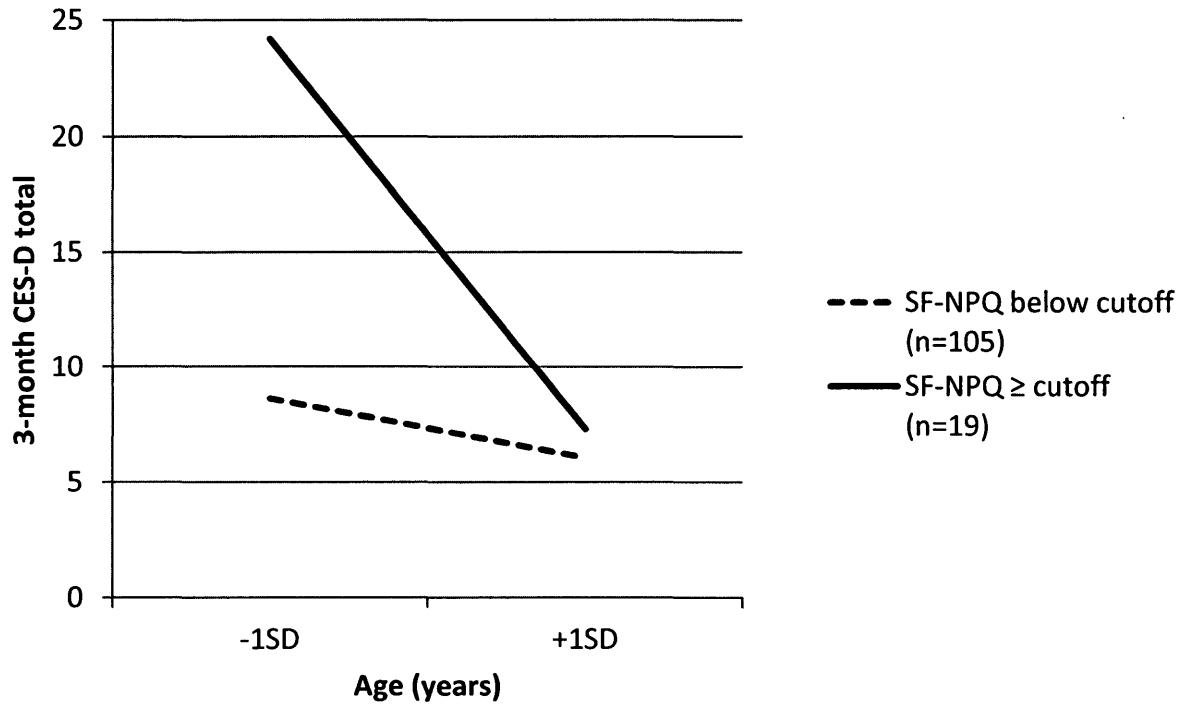

Figure 3: Interaction between age and three month SF-NPQ in relation to three month CES-D total scores.

Simple slopes analysis revealed the slope for women with neuropathic pain (SF-NPQ ≥ cutoff) three months after breast cancer surgery was significant (B= -.74 (SE = .22), β = -.82, t = -3.31, p = .001) while the slope for neuropathic pain-free women (SF-NPQ below cutoff) was nonsignficant (B = -.11 (SE = .08), β = -.13, t = -1.47, p = .15).

Notes. SF-NPQ, Neuropathic Pain Questionnaire – short-form; CES-D, Center for Epidemiologic Studies Depression scale; SD, Standard Deviation

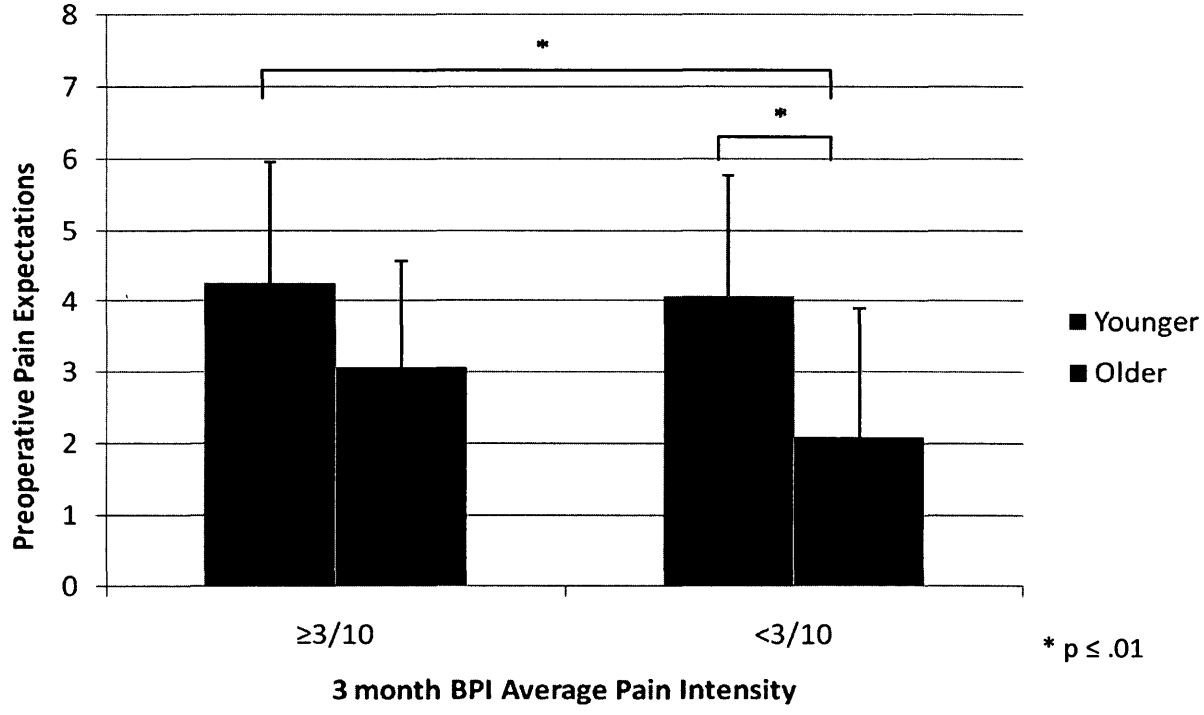

Figure 4. Preoperative pain expectations (pain immediately after surgery, after medication, and one week following surgery) of younger and older women with moderate-to-severe pain intensity and mild or no pain three months after breast cancer surgery.

* Post-hoc pairwise comparisons between younger women with moderate-to-severe pain intensity (BPI Average pain intensity ≥3/10) and younger and older women with mild or no pain (BPI Average pain intensity <3/10) ($p \leq .01$).

Note. BPI, Brief Pain Inventory.

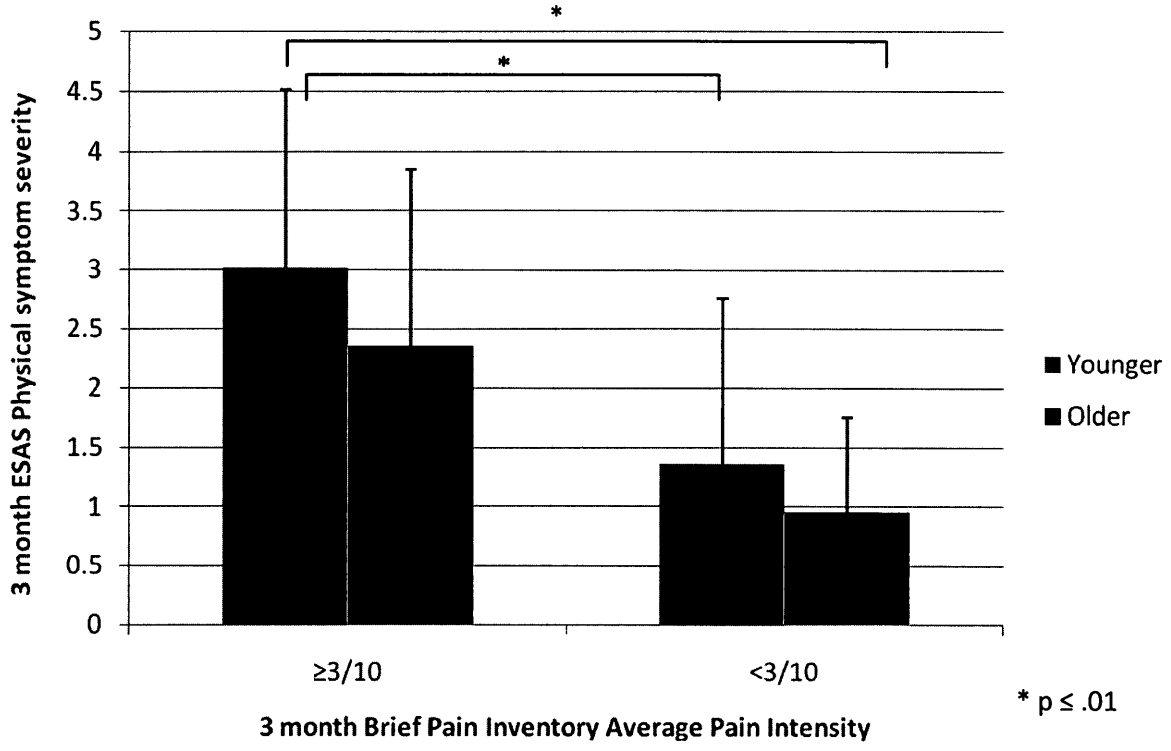

Figure 5. Three month ESAS Physical symptom severity scores of younger and older women with moderate-to-severe pain intensity and mild or no pain three months after breast cancer surgery.

* Post-hoc pairwise comparisons between younger women with moderate-to-severe pain intensity (BPI Average pain intensity ≥3/10) and younger and older women with mild or no pain (BPI Average pain intensity <3/10) ($p \leq .01$).

Note. ESAS, Edmonton Symptom Assessment Scale.

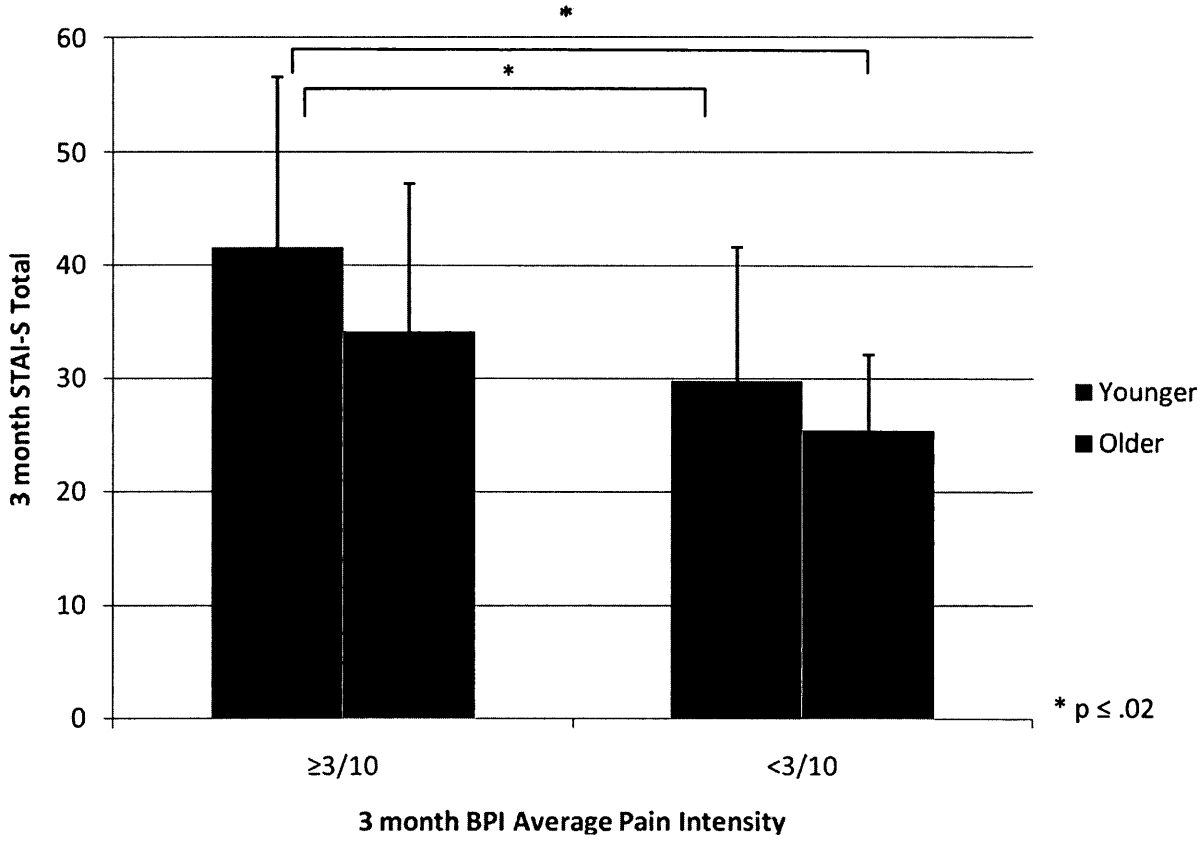

Figure 6. Three month STAI-S Total scores of younger and older women moderate-to-severe pain intensity and mild or no pain three months after breast cancer surgery.

* Post-hoc pairwise comparisons between younger women with moderate-to-severe pain intensity (BPI Average pain intensity ≥3/10) and younger and older women with mild or no pain (BPI Average pain intensity <3/10) ($p \leq .02$).

Note. STAI-S, State-Trait Anxiety Inventory – State scale.

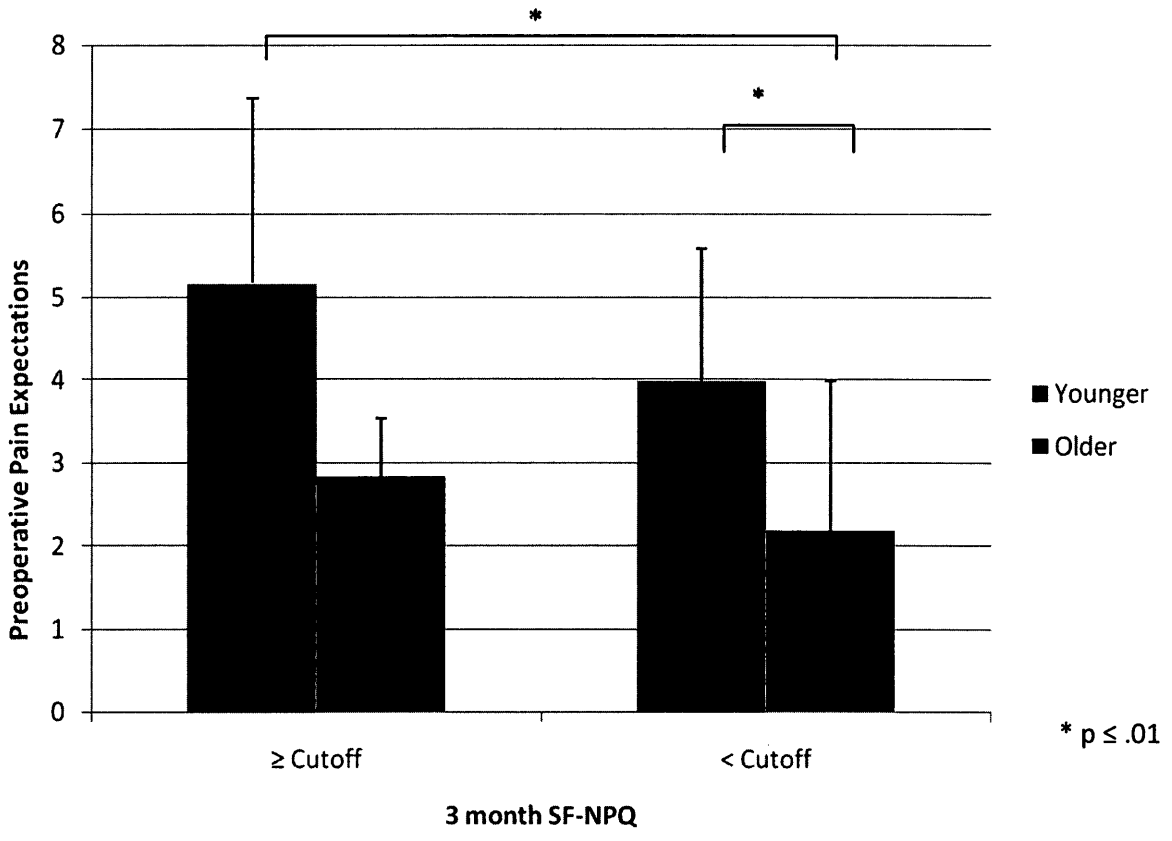

Figure 7: Preoperative pain expectations (pain immediately after surgery, after medication, and one week following surgery) of younger and older women with and without neuropathic pain three months after breast cancer surgery.

* Post-hoc pairwise comparisons between younger women with neuropathic pain (SF-NPQ ≥ cutoff) and younger and older women without neuropathic pain (SF-NPQ < cutoff) ($p \leq .01$).

Note. SF-NPQ, Neuropathic Pain Questionnaire – short form.

CHAPTER 5

General Discussion and Conclusions

Introduction

The overall aim of this dissertation was to elucidate age-related patterns in the multidimensional experience of cancer pain. To date, our understanding of the experience of cancer pain across the adult life span has been limited for several reasons. Primarily, until very recently, the biomedical model of cancer pain has been the focus of investigation (Keefe, Abernethy, & Campbell, 2005; Turk, 2002). Additionally, research into age-related patterns in cancer pain has suffered from a number of methodological limitations and has narrowly focused on pain as a unidimensional construct. Unfortunately, the undertreatment of cancer pain in older people, which was described twenty years ago (Cleeland et al., 1994), has not changed (Bernabei et al., 1998; Gao, Gulliford, & Higginson, 2011; Higginson & Gao, 2012; Yun et al., 2004). As cancer is a disease of older people (Canadian Cancer Society [CCS], 2013), with the aging population (Statistics Canada, 2007), the numbers of older people who will need proper pain management will grow. We face an emerging healthcare crisis if we do not significantly improve our understanding of cancer pain across the adult life span.

The studies described in this dissertation have begun to improve our understanding of the experience of cancer pain across the adult life span. Proper pain assessment is fundamentally important to pain management. Consequently, a multidimensional measure of cancer pain qualities was validated for use in older and younger cancer patients (Chapter 2). This permitted the use of the measure to investigate age-related patterns in the multidimensional experience of cancer pain and its correlates (Chapter 3). The role of pain in the relationship between age and depression was

clarified in a preliminary way (Chapter 4). This final Chapter will attempt to integrate the findings of these studies and suggest directions for future research and implications for treatment.

Pain Assessment: Validating the Short-Form-McGill Pain Questionnaire for use in Older and Younger People with Cancer

Pain assessment is a necessary component of pain management, and conversely, improper assessment is one of the major contributors to improper pain management (Gauthier & Gagliese, 2011). An essential consideration in selecting an assessment tool for assessing age-related patterns is whether it can be completed by all age groups (Streiner & Norman, 2008). When comparing responses on a tool, it is also essential that it measures the same thing the same way across age groups (G. W. Cheung & Rensvold, 2002; G. W. Cheung & Lau, 2012). This is important, because if an age difference is detected, it may be interpreted as a possible age-related effect, rather than as differences in the psychometric properties of the tool. Although there are unidimensional measures of pain intensity, such as Numeric Rating Scales (NRS), that have been validated for use across the adult life span (Gauthier & Gagliese, 2011), multidimensional measures of pain quality allow for a more comprehensive assessment of the characteristics of pain (Gauthier & Gagliese, 2011). The McGill Pain Questionnaire (Melzack, 1975) is the most widely used measure of the multidimensional qualities of pain. It has been recently revised and expanded (Dworkin et al., 2009): The Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2) includes 11-point NRSs and six new qualities that assess neuropathic pain. This is especially relevant to people with cancer, as a substantial

proportion of patients may experience neuropathic pain (Bennett et al., 2012; Caraceni & Portenoy, 1999; Grond, Zech, Diefenbach, Radbruch, & Lehmann, 1996).

Importantly, older and younger cancer patients were equally able to use the SF-MPQ-2 (Chapter 2). Consistent with previous studies (Dworkin et al., 2009; Lovejoy, Turk, & Morasco, 2012), a four-factor solution emerged, consisting of items assessing the Continuous, Intermittent, Neuropathic and Affective qualities of pain. Construct validity was very similar across age groups: The same items loaded on the same subscales in the same way, although there were somewhat stronger correlations between two of the subscales among older than younger patients. Convergent validity was equally good across age groups, although the strength of the correlation between the Continuous subscale and the measure of mental health quality of life was stronger in older than younger patients. However, given the weight of the evidence, despite these small age differences, the SF-MPQ-2 is valid for use in younger and older people with cancer pain. Interestingly, older and younger patients chose the same number of words overall and the same number of sensory words to describe their pain. This is in contrast with studies of older patients with chronic nonmalignant pain who chose fewer words than younger people to describe their pain (Gagliese & Melzack, 1997a; Gagliese & Melzack, 2003). It is possible that the inclusion of NRSs in the new construction of the SF-MPQ-2 may contribute to a different response style among older people or that the characteristics of cancer pain override the previously documented parsimonious response style of older people. Studies examining the use of the SF-MPQ-2 in older and younger people with chronic nonmalignant pain may clarify these inconsistencies.

Age-Related Patterns in Cancer Pain

Consistent with studies of people with chronic nonmalignant pain that have shown that older and younger people choose the same words most frequently to describe their pain (Gagliese & Melzack, 2003), older and younger patients chose the same words – aching pain, tiring-exhausting, sharp pain, and dull pain – most often to describe their pain. Also, there were no age differences in the intensity of each selected word (Chapter 2), or the intensity of pain on average, or interference from pain (Chapter 3), suggesting that cancer pain may feel the same, hurt just as much, and interfere in important daily activities and psychological wellbeing to a similar extent in older and younger people. Taken together, these data refute the claims that older people may be more reluctant to report pain (Yong, Bell, Workman, & Gibson, 2003) or less likely to endorse intense pain than younger people (Greenwald, 1991; Nicholas, Asghari, & Blyth, 2008; Oberle, Paul, Wry, & Grace, 1990).

Despite these similarities, older people were somewhat less likely to receive an opioid prescription than younger people, and there were subtle differences in the relationships of pain interference to treatment factors across age groups. Receipt of an opioid prescription was associated with higher pain interference in older, but not younger patients, whereas taking a greater number of analgesics of any class was associated with higher pain interference in younger, but not older patients. These findings suggest that healthcare providers may respond to cues differently from older and younger patients. In older people, who may be less likely to be prescribed an opioid, greater verbal reports or nonverbal displays of pain interference may result in the provision of an opioid.

However, in younger people, greater verbal reports or nonverbal displays of pain interference may result in the provision of more analgesic treatment overall. Studies investigating this possibility are urgently needed to gain a better understanding of the underlying causes of the undertreatment of cancer pain in older patients (Bernabei et al., 1998; Cleeland et al., 1994; Gao, Gulliford, & Higginson, 2011; Higginson & Gao, 2012; Yun et al., 2004).

Consistent with findings from the chronic nonmalignant pain literature (Cook, Brawer, & Vowles, 2006; Edwards, 2006; McIlvane, Schiaffino, & Paget, 2007; Turk, Okifuji, & Scharff, 1995), age differences in the correlates of pain outcomes were present in the absence of age differences in the outcomes themselves (Gagliese, 2009). The presence of comorbidity was associated with greater pain for younger, but not older people, while the presence of chronic nonmalignant pain was associated with greater pain for older, but not younger people. Other health status factors operated differently across age groups in the relationship between pain catastrophizing and pain interference, suggesting a supportive context that may be unique to older than younger people and which may be consistent with a Communal Coping Model of catastrophizing (Sullivan, Thorn, Haythorntwaite, Keefe, Martin, Bradley, & Lefebvre, 2001). The possibility that healthcare providers might respond differently to older and younger people's pain interference cues may have implications for treatment. It is therefore important that we gain a better understanding of age-related patterns in the supportive context of cancer pain.

Depressive symptoms did not differ across age groups. In fact, more than half of older and younger people with advanced cancer scored above a cutoff which may indicate clinically relevant symptomatology, suggesting that depressive symptoms were highly prevalent in this sample, regardless of age. However, distress in the form of intrusive thoughts was associated with greater pain among younger but not older people, a finding which may be consistent with those of the qualitative study, where younger people had difficulty adapting to cancer pain and grieved the loss of their pre-pain selves, while older people adapted by accepting pain and retaining or modifying important activities (Gagliese et al., 2009). Life span developmental theory suggests that our ability to adapt to lifecourse disruptions, such as pain in the context of advanced cancer, is affected by a host of biopsychosocial factors (Aldwin, Spiro, & Park, 2006). It may be that older peoples' prior experience with health limitations confers an adaptive advantage, whereas younger people, who may perceive cancer and pain as developmentally off-time (Gagliese et al., 2009; Revenson & Pranikoff, 2005), may have difficulty adapting. Younger people with comorbidity may have the most difficulty. These findings have significant clinical utility and demonstrate that even though older and younger people may present with similar ratings of pain, the factors that contribute to their overall experience of pain may differ.

It has been suggested that age should not be a consideration when offering multidisciplinary treatments for pain (Sorkin, Rudy, Hanlon, Turk, & Stieg, 1990). Indeed, there is evidence that older people may benefit from such treatments (Gagliese & Melzack, 1997c). The findings presented in this dissertation present compelling evidence

that age should be a factor when *tailoring* these treatments. However, we have only begun to elucidate age-related patterns in the experience of cancer pain. Much future research is needed to understand how these treatments should be designed for older and younger patients across the cancer continuum.

The Moderating Role of Pain in the Relationship between Age and Depressive Symptoms

In studies of cancer patients that do not consider pain, younger age is associated with greater depressive symptoms (Compas et al., 1999; Kroenke et al., 2004; Politi, Enright, & Weihs, 2007; Schroevers, Ranchor, & Sanderman, 2004; Vinokur, Threatt, Vinokur-Kaplan, & Satariano, 1990; Wenzel et al., 1999). As described above, younger people may view cancer as developmentally off-time and as a threat to their ability to attain life goals, whereas older people may experience a unique adaptive benefit of prior experience with health limitations (Gagliese et al., 2009; Schulz & Heckhausen, 1996; Chapter 3). However, the presence of cancer pain may operate as a risk factor for depressive symptoms to the same extent in older and younger patients (Chapters 3 and 4). These findings are consistent with prior studies of people with cancer pain where age has not been associated with depressive symptoms (Gagliese, Gauthier, & Rodin, 2007; Green & Hart-Johnson, 2010; Kai-hoi Sze, Wong, Lo, & Woo, 2000; Knotkova, Clark, Mokrejs, Padour, & Kuhl, 2004; G. M. Williamson & Schulz, 1995). This suggests that interventions addressing pain and depressive symptoms are important for patients across the adult life span. Interestingly, neuropathic pain may be associated with greater depression among younger, but not older people (Chapter 4), which may suggest a

possible age-related pattern in the correlates of depressive symptoms related to the pain's underlying etiology. This fascinating possibility requires further research.

Integrating the Findings

There were no age differences in pain intensity, qualities or interference. However, there were age-related patterns in relationships between variables. For example, the SF-MPQ Continuous subscale was more strongly associated with mental health quality of life in older than younger patients (Chapter 2) and there were several age-related patterns in the correlates of cancer pain outcomes (Chapter 3). These data are consistent with studies of people with chronic nonmalignant pain that demonstrate that even if there are no age differences on factors like pain or depressive symptoms, there may be age-related patterns in the relationships between factors (Cook, Brawer, & Vowles, 2006; Edwards, 2006; McIlvane, Schiaffino, & Paget, 2007; Turk, Okifuji, & Scharff, 1995). Taken together, these findings strongly suggest the need for the development of multimodal age-tailored treatments. In this dissertation, the most salient factors that are important to the experience of cancer pain among older and younger people have begun to emerge, but more research is needed to identify how to effectively tailor treatments.

It has been suggested that older people are less psychologically affected by cancer than younger people (Blank & Bellizzi, 2008). The data presented in this dissertation suggest that this is not the case among people with cancer pain. There were no age differences in the intensity and prevalence of depressive symptoms among people with advanced cancer and pain (Chapter 3), and age was not associated with depressive

symptoms in women who reported moderate-to-severe pain intensity three months after breast cancer surgery (Chapter 4). These findings present convincing evidence of the need to address depressive symptoms and pain in older and younger patients.

While neuropathic pain was associated with greater depressive symptoms to the same extent in older and younger people with advanced cancer (Chapter 3), neuropathic pain three months after breast cancer surgery seemed to operate as a risk factor for greater depressive symptoms in younger, but not older women (Chapter 4). A number of possible explanations for these inconsistent findings may be considered. First, different scales were used in each study to assess neuropathic pain. We have shown that the psychometric properties of the SF-MPQ-2 are not age-related (Chapter 2). Although the Neuropathic Pain Questionnaire-short-form (SF-NPQ [Backonja & Krause, 2003]) used in Chapter 3 has been shown to discriminate between neuropathic and non-neuropathic cancer pain (Mercadante et al., 2009), age-related consistency in its psychometric properties remain to be demonstrated. Therefore, it is unclear whether this may account for the inconsistencies across studies. It is also unclear whether the same results would have been obtained if we had used the SF-MPQ-2 in Chapter 4.

Cross-study participant differences should also be considered. On the one hand, Chapters 2 and 3 reported on men and women with different primary cancers who experienced pain for approximately one year. On the other hand, Chapter 4 reported on women three months after surgery for earlier stage breast cancer. In other patient populations, women may be more likely than men to report neuropathic pain (Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009; Mogil, 2012). However, in

people with cancer pain, sex differences in neuropathic pain have not been found (Grond et al., 1999). Unfortunately, studies comparing neuropathic pain in men and women matched for cancer type are not available; therefore, the relevance of potential sex differences remains unclear. Several other possibilities, including gonadal hormone effects (Kuba & Quinones-Jenab, 2005; Rehman & Masson, 2005) and different manifestations of neuropathic pain across different samples (e.g. postoperative pain vs. pain of different etiologies) may render cross-study comparisons inappropriate.

Substantive Contributions

The findings from this dissertation improve our understanding of the experience of cancer pain across the adult life span and make a significant contribution to the literature. The validation of the SF-MPQ-2 was an essential first step in achieving the overall aim of the dissertation (Chapter 2). The validation study provides important information about the utility of a multidimensional measure of pain qualities in people with cancer pain of all ages, which will benefit future research and may improve clinical care. There are a number of other novel findings: This dissertation presents the first study to demonstrate that the qualities of cancer pain are the same and the intensity of each selected quality is the same in older and younger people (Chapter 2). Despite a lack of age differences in pain outcomes, consistent with studies of people with chronic nonmalignant pain (Cook, Brawer, & Vowles, 2006; Edwards, 2006; McIlvane, Schiaffino, & Paget, 2007; Turk, Okifuji, & Scharff, 1995), there were age-related patterns in the correlates of pain that spanned the biopsychosocial spectrum. This study is the first to identify different profiles of health status risk factors – e.g. comorbidity

among younger, but not older people, and chronic nonmalignant pain among older, but not younger people – as risk factors for poor pain outcomes. It is also the first study to identify a unique role of health status factors that may impact on the supportive context of cancer pain differently for older and younger people. Moreover, despite a lack of age differences in cancer pain intensity, qualities, or interference, there may be subtle age differences in the way healthcare providers respond to patients' reports or displays of pain-related interference (Chapter 3) which may help to explain the pervasive undertreatment of pain in older people (Bernabei et al., 1998; Cleeland et al., 1994; Gao, Gulliford, & Higginson, 2011; Higginson & Gao, 2012; Yun et al., 2004). Furthermore, consistent with the literature (Gagliese, Gauthier, & Rodin, 2007; Green & Hart-Johnson, 2010; Kai-hoi Sze, Wong, Lo, & Woo, 2000; Knotkova, Clark, Mokrejs, Padour, & Kuhl, 2004; G. M. Williamson & Schulz, 1995), older and younger people with pain do not differ in the severity of depressive symptoms or the prevalence of clinically significant levels of depression (Chapters 3 and 4), but there may be something unique about neuropathic pain after breast cancer surgery that puts younger but not older women at risk for greater depressive symptoms (Chapter 4).

The studies described in this dissertation substantially improve on the methodological limitations of the existing literature. Chapter 3 describes the first study of age-related patterns in the experience of cancer pain to adopt a multidimensional operationalization of cancer pain, which is important, because and relying on intensity alone insufficiently describes this experience (Jensen & Karoly, 2011). Due to the inclusion criteria, prevalence was not confounded with intensity, an issue present in some

prior studies of age-related patterns in cancer pain intensity (e.g. Jordhoy et al., 2001; Mohile et al., 2011; Rustoen et al., 2003; Stuver et al., 2012; G. M. Williamson & Schulz, 1995; Wilson et al., 2009). This study is also the first to match participants based on sex and primary tumor type. These factors have been associated with pain (Dobratz, 2008; Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009; Grond, Zech, Diefenbach, Radbruch, & Lehmann, 1996; Miaskowski, 2004; Vainio & Auvinen, 1996); therefore, this is an important methodological strength. Additionally, older people with comorbidities have traditionally been excluded from clinical trials (Dale et al., 2012), a practice which compromises external validity. The inclusion of people with comorbidities and chronic nonmalignant pain (Chapters 2 and 3) and women with pain prior to surgery (Chapter 4) enhances external validity and paints a clear picture of patients who are seen in everyday clinical practice.

This dissertation has provided important information clarifying and refining the experience of cancer pain in older and younger people. It is clear that the age-related patterns in the correlates of cancer pain outcomes span the biopsychosocial spectrum and that these factors interact with each other to impact on pain outcomes in different ways for older and younger people. For example, certain health status factors, like functional status and severity of other cancer symptoms, may operate on the supportive context of cancer pain differently for older and younger patients. Other health status factors, like comorbid conditions, may also provide unique adaptive advantages for older, but not younger patients. It will be important for future studies of age-related patterns in cancer pain to consider these complex interactions.

Future Directions and Implications for Clinical Care

The findings described in this dissertation have considerable heuristic value and a number of future research directions are evident. Primarily, cancer pain is dynamic and may fluctuate as the disease progresses or remits, or as patients proceed through treatments, such as surgery, chemotherapy, and radiation (Bruera & Kim, 2003; Burton, Fanciullo, Beasley, & Fisch, 2007; McCarthy, Phillips, Zhong, Drews, & Lynn, 2000; Paice, 2011; Peng, Wu, Sun, Chen, & Huang, 2006). Longitudinal studies are needed to track age-related patterns in the progression of pain throughout the course of treatment or as the disease progresses or remits. Dyadic studies that include patients and their caregivers are needed to test the potential unique role of health status factors on the supportive context of cancer among older patients. Studies are also needed to identify whether healthcare providers respond to verbal and/or nonverbal cues differently from older and younger patients when making treatment decisions. Such studies would have considerable clinical relevance and may further contribute to understanding the underlying causes of the undertreatment of cancer pain in older people (Bernabei et al., 1998; Cleeland et al., 1994; Gao, Gulliford, & Higginson, 2011; Higginson & Gao, 2012; Yun et al., 2004).

It is surprising that comorbidity has been virtually ignored in younger cancer patients. Much further work is needed to assess the role of comorbidities, chronic nonmalignant pain and other health status factors in the context of cancer pain. Future studies may need to expand the conceptualization of burden beyond comorbidity to include a more nuanced assessment that includes painful comorbidities (Dominick, Blyth,

& Nicholas, 2012), symptom burden and functional status. This may have implications for the refinement of frailty definitions, on which consensus remains to be reached (Balducci & Extermann, 2000; Hamaker et al., 2012; Ruiz, Reske, Cefalu, & Estrada, 2013), and Comprehensive Geriatric Assessments, which have yet to be standardized and which rarely consider pain (Horgan et al., 2012; Puts et al., 2012).

High preoperative pain expectations was an important predictor of pain three months after breast cancer surgery for both older and younger women (Chapter 4). In previous studies, older age has been associated with lower preoperative pain expectations (Gagliese, Jackson, Ritvo, Wowk, & Katz, 2000; Schnur et al., 2007). Given this and the importance of this preoperative factor to postoperative outcomes for women regardless of age, future research is needed to identify age-related predictors of pain expectations and to identify interventions to address excessively high expectations of pain prior to surgery in older and younger women.

Conclusions

This dissertation has demonstrated that cancer pain may feel the same, hurt just as much, and interfere with important life activities and wellbeing to the same extent in older and younger people. Nonetheless, despite a lack of age differences in cancer pain, there may be subtle treatment differences that may contribute to the undertreatment of pain in older people. Older and younger people with pain may be equally at risk for depressive symptoms. Although there are some similarities, there are also age differences in the correlates of pain outcomes which span the biopsychosocial spectrum. These findings suggest age-tailored treatments for cancer pain may be warranted and future

research is needed to further clarify age-related patterns in the experience of cancer pain across the disease continuum.

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APPENDIX A

Research Ethics Board Approvals

University Health Network
Toronto General Toronto Western Princess Margaret

University Health Network
Research Ethics Board
10th Floor, Room 1056
700 University Ave
Toronto, Ontario, M5G 1Z5
Phone: (416) 581-7849

Notification of REB Continued Approval

Date: April 5th, 2013
To: Dr. Lucia Gagliese
Rm 236A, 9th Floor, North Wing, Eaton, Toronto General Hospital, 200 Elizabeth St.

Re: 06-0182-AE
Biopsychosocial Age Differences in the Experience of Cancer Pain

REB Review Type:	Expedited
REB Initial Approval Date:	April 20th, 2006
REB Annual Approval Date:	April 20th, 2013
REB Expiry Date:	April 20th, 2014

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement, ICH Good Clinical Practice Guidelines, Ontario Personal Health Information Protection Act (2004), Part 4 of the Natural Health Product Regulations and Part C, Division 5 of the Food and Drug Regulations of Health Canada.

Best wishes on the successful completion of your project.

Sincerely,

Leda Ivic Weiss, MSc
Research Ethics Coordinator

For: Anna Gagliardi, PhD
Co-Chair, University Health Network Research Ethics Board

MOUNT SINAI HOSPITAL

Research Ethics Board

600 University Avenue, Room 19-311
Toronto, Ontario, Canada, M5G 1X5
t: (416) 586-4875 f: (416) 586-4715
www.mtsinai.on.ca

Notification of REB Continued Approval

Date: December 21, 2012

To: Dr. Lucia Gagliese
University Health Network (Toronto General)
200 Elizabeth Street EN 9-236-A
Toronto, Ontario M5G 2C4 Canada

Re: 08-0244-E
Biopsychosocial Age Differences in the Experience of Cancer Pain

REB Review Type:	Expedited
REB Initial Approval Date:	28 November, 2008
REB Expiry Date:	28 November, 2013
Consent Form(s) Currently Approved for Use:	Consent Form (Dated: 06/04/2010)

The above-named study has received continued approval from the Mount Sinai Hospital Research Ethics Board until the expiry date noted above. Additionally, the REB has approved the above mentioned consent form. If the study is expected to continue beyond the expiry date, you are responsible for ensuring the study receives re-approval. The REB must also be notified of the completion or termination of this study and a final report provided.

If, during the course of the research, there are any serious adverse events, confidentiality concerns, changes in the approved project, or any new information that must be considered with respect to the project, these should be brought to the immediate attention of the REB. In the event of a privacy breach, you are responsible for reporting the breach to the MSH REB and the MSH Corporate Privacy Office (in accordance with Ontario health privacy legislation – Personal Health Information Protection Act, 2004). Additionally, the MSH REB requires reports of inappropriate/unauthorized use of the information. As the Principal Investigator, you are responsible for the ethical conduct of this study.

The MSH Research Ethics Board operates in compliance with the Tri-Council Policy Statement 2, ICH/GCP Guidelines and Part C, Division 5 of the Food and Drug Regulations of Health Canada.

Sincerely,

Nushrat Sultana, B.Sc., CCRP
Ethics Coordinator, Research Ethics Board

For: Ronald Heslegrave, Ph.D.
Chair, Mount Sinai Hospital Research Ethics Board

YORK
UNIVERSITÉ
UNIVERSITY

OFFICE OF
RESEARCH
ETHICS (ORE)

5th Floor,
York Research Tower,
4700 Keele St.
Toronto ON
Canada M3J 1P3
Tel 416 736 5914
Fax 416 650 8197
www.research.yorku.ca

RENEWAL

Certificate #:	**2010 - 104**
2nd Renewal Approved:	**05/08/12**
Renewal Approved:	**04/15/11**
Approval Period:	**05/08/12-05/08/13**

Memo

To: Dr. Lucia Gagliese, Faculty of Health, lucia.gagliese@uhn.on.ca

From: Alison M. Collins-Mrakas, Sr. Manager and Policy Advisor, Research Ethics
(on behalf of Wade Cook, Chair, Human Participants Review Committee)

Date: **Tuesday May 8th, 2012**

Re: Ethics Approval

Biopsychosocial Age Differences in the Experience of Cancer Pain

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With respect to your research project entitled, "Biopsychosocial Age Differences in the Experience of Cancer Pain", the committee notes that, as there are no substantive changes to either the methodology employed or the risks to participants in and/or any other aspect of the research project, renewal of approval of the above-noted protocol is granted.

Should you have any questions, please feel free to contact me at: 416-736-5914 or via email at: acollins@yorku.ca.

Yours sincerely,

Alison M. Collins-Mrakas M.Sc., LLM
Sr. Manager and Policy Advisor,
Office of Research Ethics

University Health Network
Toronto General Toronto Western Princess Margaret

University Health Network
Research Ethics Board
10th Floor, Room 1056
700 University Ave
Toronto, Ontario, M5G 1Z5
Phone: (416) 581-7849

Notification of REB Continued Approval

Date: January 22nd, 2013
To: Dr. Lucia Gagliese
Rm 236A, 9th Floor, North Wing, Eaton, Toronto General Hospital
200 Elizabeth St.
Toronto, Ontario, Canada
M5G 2C4

Re: 07-0553-AE
Age-Related Patterns in Pain Following Breast Cancer Surgery

REB Review Type:	Expedited
REB Initial Approval Date:	January 28th, 2008
REB Annual Approval Date:	January 28th, 2013
REB Expiry Date:	January 28th, 2014

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement, ICH Good Clinical Practice Guidelines, Ontario Personal Health Information Protection Act (2004), Part 4 of the Natural Health Product Regulations and Part C, Division 5 of the Food and Drug Regulations of Health Canada.

Best wishes on the successful completion of your project.

Sincerely,

M. Mistry

Meenal Mistry, BSc
Research Ethics Coordinator

For: Anna Gagliardi, PhD
Co-Chair, University Health Network Research Ethics Board

YORK
UNIVERSITÉ
UNIVERSITY

OFFICE OF
RESEARCH
ETHICS (ORE)

5th Floor,
York Research Tower,
4700 Keele St.
Toronto ON
Canada M3J 1P3
Tel 416 736 5914
Fax 416 650 8197
www.research.yorku.ca

RENEWAL

Memo

Certificate #:	**2012 - 129**
Renewal Approved:	**04/17/13**
Approval Period:	**04/17/13-04/17/14**

To: Professor Lucia Gagliese, Faculty of Health, lucia.gagliese@uhn.ca

From: Alison M. Collins-Mrakas, Sr. Manager and Policy Advisor, Research Ethics
(on behalf of Duff Waring, Chair, Human Participants Review Committee)

Date: Wednesday April 17th, 2013

Re: **Ethics Approval**

Age Related Patterns in Pain Following breast Cancer Surgery

With respect to your research project entitled, "Age Related Patterns in Pain Following breast Cancer Surgery", the committee notes that, as there are no substantive changes to either the methodology employed or the risks to participants in and/or any other aspect of the research project, a renewal of approval re the above project is granted

Should you have any questions, please feel free to contact me at: 416-736-5914 or via email at: acollins@yorku.ca.

Yours sincerely,

Alison M. Collins-Mrakas M.Sc., LLM
Sr. Manager and Policy Advisor,
Office of Research Ethics

APPENDIX B

Consent Forms

CONSENT FORM - UHN

TITLE: Biopsychosocial Age Differences in the Experience of Cancer Pain

INVESTIGATOR: Dr. Lucia Gagliese (Telephone: 416-340-4296)

SPONSOR: Canadian Institutes of Health Research

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks, and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don't understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing this document.

Background and Purpose

The purpose of this study is to develop an understanding of thoughts and feelings related to pain. We would like to know how people deal with pain

and how pain impacts on people's well being. You have been identified by your doctor as a potential participant in this cancer study that will examine your experience of pain, its impact on your life and how you cope with it. If you consent, we will ask you to complete a set of questionnaires. A total of 300 participants of different ages are planned to take part in this study over the next 24 months.

Procedures

If you agree to participate in this study, you will be asked some questions about your memory. You will be given a questionnaire package that takes approximately one (1) hour to complete. This questionnaire asks about your pain, how your pain impacts on your life, and your general health. Other parts of the questionnaire will ask you about personal information, such as your marital status and personal relationships. You have the option to complete the questionnaires on your own, or with the help from a research team member. You may complete the questionnaires at the hospital or if you prefer, you may take the questionnaire package home and return them by mail once they are completed (we will provide postage and an envelope for this purpose). If you do choose to participate and take the questionnaire package home, we will telephone you in two weeks to remind you to mail your completed questionnaire package. You are under no obligation to answer questions that you do not wish to answer, and you may feel free to take breaks as required.

Risks

There are no known risks to you for participation in this study. The researchers involved in this study will make every effort to keep your personal information secure. Your information will be stored and protected in a locked facility, however your confidentiality cannot be guaranteed.

Benefits

This study may not benefit you directly but it may improve future pain management for individuals experiencing cancer pain.

Confidentiality

All information obtained during the study is completely confidential. You will be identified with a study number. No names or identifying information will be used in any publications or presentations.

Your health record will be reviewed to verify that we have accurate information regarding your health history. Certain sections of your chart (such as medication records) will be photocopied and included in your research chart for reference and evaluation. All of these photocopies will be completely confidential and any identifying information will be blacked out.

Participation

Your participation in this study is voluntary. You can choose not to participate or you may withdraw at any time without affecting your medical care.

Payment

You will be reimbursed for any additional parking fees or transportation costs you might incur as a result of participation in this study.

Compensation

If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. The reasonable costs of such treatment will be covered by your health insurance for any injury or illness that is directly a result of participation in this study. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities.

Questions

If you suffer any side effects or other injuries during this study, or if you have any general questions about the study, please call Dr. Lucia Gagliese at 416-340-4296.

If you have any questions about your rights as a research participant, please call the University Health Network Research Ethics Board at 416-581-7849. They are not involved with the research project in any way and calling them will not affect your participation in the study. You may also contact the York University Human Participants Review Sub-Committee at 416-736-5055 (Office of Research Ethics, 5th Floor, York Research Tower) if you have questions about your rights as a research participant.

Consent

I have had the opportunity to discuss this study and my questions have been answered to my satisfaction. I consent to take part in the study with the understanding I may withdraw at any time without affecting my medical care. I have received a signed copy of this consent form. I voluntarily consent to participate in this study.

_____	_____	_____
Patient's Name (Please Print)	Patient's Signature	Date

I confirm that I have explained the nature and purpose of the study to the patient named above. I have answered all questions.

_____	_____	_____
Name of Person Obtaining Consent	Signature	Date

CONSENT TO PARTICIPATE IN A RESEARCH STUDY - MSH

Title Biopsychosocial Age Differences in the Experience of Cancer Pain

Investigator Dr. Lucia Gagliese (Telephone: 416-340-4296)

Co-Investigators Dr. G. Rodin, Dr. C. Zimmermann, Dr. M. Moore, Dr. F. Shepherd, Dr. L. Librach

Sponsor Canadian Institutes of Health Research

Introduction

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks, and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don't understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing this document.

Background and Purpose

The purpose of this study is to develop an understanding of thoughts and feelings related to pain. We would like to know how people deal with pain and how pain impacts on people's well being. You have been identified by your doctor as a potential participant in this cancer study that will examine your experience of pain, its impact on your life and how you cope with it. If you consent, we will ask you to complete a set of questionnaires. A total of 300 participants of different ages are planned to take part in this study over the next 24 months from two places. About 100 people will come from Mount Sinai Hospital.

Study Design and Procedure

If you agree to participate in this study, you will be asked some questions about your memory. You will be given a questionnaire package that takes approximately one (1) hour to complete. This questionnaire asks about your pain, how your pain impacts on your life, and your general health. Other parts of the questionnaire will ask you about personal information, such as your marital status and personal relationships. You have the option to complete the questionnaires with help from a research team member or on your own. If you wish to complete the questionnaires on your own, you may return them by mail once they are completed (we will provide postage and an envelope for this purpose). If you do choose to participate and complete the questionnaires on your own, we will telephone you in two weeks to remind you to mail your completed questionnaire package. You are under no obligation to answer questions that you do not wish to answer, and you may feel free to take breaks as required.

Risks Related to Being in the Study

There are no known risks to you for participation in this study. The researchers involved in this study will make every effort to keep your personal information secure. Your information will be stored and protected in a locked facility, however your confidentiality cannot be guaranteed.

Benefits to Being in the Study

This study may not benefit you directly but it may improve future pain management for individuals experiencing cancer pain.

Confidentiality

All information obtained during the study is completely confidential. You will be identified with a study number. No names or identifying information will be used in any publications or presentations.

Your health record will be reviewed to verify that we have accurate information regarding your health history. Certain sections of your chart (such as medication records) will be photocopied and included in your research chart for reference and evaluation. All of these photocopies will be completely confidential and any identifying information will be blacked out.

Voluntary Participation

Your participation in this study is voluntary. You can choose not to participate or you may withdraw at any time without affecting your medical care.

In Case You Are Harmed in the Study

If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. The reasonable costs of such treatment will be covered by your health insurance for any injury or illness that is directly a result of participation in this study. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities.

Questions About the Study

If you suffer any side effects or other injuries during this study, or if you have any general questions about the study, please call Dr. Lucia Gagliese at 416-340-4296.

If you have any questions about your rights as a research participant, please call Dr. Ronald Heslegrave, Ph. D., Chair of the Mount Sinai Hospital Research Ethics Board (REB) or the Research Ethics office number at 416-586-4875. This person is not involved with the research project in any way and calling him will not affect your participation in the study. You may also contact the York University Human Participants Review Sub-Committee at 416-736-5055 (Office of Research Ethics, 5th Floor, York Research Tower) if you have questions about your rights as a research participant.

Consent

I have had the opportunity to discuss this study and my questions have been answered to my satisfaction. I consent to take part in the study with the understanding I may withdraw at any time without affecting my medical care. I have received a signed copy of this consent form. I voluntarily consent to participate in this study.

_____	_____	_____
Patient's Name (Please Print)	Patient's Signature	Date

I confirm that I have explained the nature and purpose of the study to the patient named above. I have answered all questions.

_____	_____	_____
Name of Person Obtaining Consent	Signature	Date

CONSENT FORM

TITLE: **Age-related patterns in pain following breast cancer surgery.**

INVESTIGATOR: Dr. Lucia Gagliese, Toronto General Hospital

(Telephone: 416-340-4296)

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don't understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing this document.

Background and Purpose

Surgery is one of the treatments for breast cancer with removal of local tumour tissue (lumpectomy) and of surrounding tissues in which the tumour might be present being the most common procedures. There is little information available regarding age, levels of pain and analgesic use in women who undergo these types of surgeries. As a patient who will have breast surgery, you are being asked if you would like to participate in a study that will look at sensitivity to pain and recovery throughout your surgical experience in relation to your age. Past research has shown that inflammatory substances (cytokines) and some natural hormones (estrogen and progesterone) produced in your body may change how sensitive you are to pain. 250 women will participate from University Health Network. This study will last approximately 5 years. Participation for each person will last approximately two years in total.

Procedures

Preadmission visit

If you agree to participate in this study, you will be asked to complete several questionnaires about your mood, pain history, medical history, activity levels and overall well-being. You will also be asked if you are taking any medications for pain or any other reason.

You will then undergo a functional assessment, which measures shoulder range of motion, hand grip strength, and arm circumference. In addition, the research assistant will assess your sensitivity to pain (pain threshold) using brief tests of heat, pressure, and pricking stimulation. You will be asked to say "stop" as soon as you feel pain. A blood sample will be drawn at this time to assess your cytokine levels. You will be given a questionnaire package to complete at home and return on the day of surgery. Your preadmission visit will take approximately 35 minutes to complete. Similar to your surgeon's instructions, we ask that you not eat for 12 hours prior to your surgery and that you avoid strenuous physical exercise and alcohol for 2 days prior to surgery. You will receive a telephone reminder of these instructions 2 days before your surgery. The results of your routine pre-operative blood tests, ordered by your surgeon, also will be reviewed and collected for the study.

Day of surgery

Before Surgery

On the day of surgery blood will be drawn to assess cytokine, estrogen and progesterone levels. Measures of pain, mood, symptoms, pain medication consumption, and pain threshold will be taken. Many of these are similar to those previously completed.

During Surgery

Your surgery will be performed as usual under general anesthesia (i.e., you will be asleep for the duration of the operation). Information (e.g., medication use, blood loss, surgical duration, complications) will be recorded from your medical chart.

After Surgery

Standard of care is not changed if you participate in this study. That means you will receive the same pain medicine and other types of care whether or not you participate in this study.

At 6 hours after surgery, you will be asked about your pain level and any side effects you may have experienced. Information regarding your pain medication will also be collected. This visit will take approximately 10 minutes.

Following your surgery, at either 24 h, 48 h or 72 hours, you will be asked questions about your pain, memory, mood, and well-being, as well as questions regarding your satisfaction with your pain treatment. You will be asked to repeat the tests to measure your sensitivity to pain. Blood will be taken to measure levels of cytokines, estrogen, progesterone and morphine (the medication you will be using to control your pain). All medication use will be recorded from your medical chart. This visit will take approximately 45 minutes.

Follow-up

Follow-up Assessments (1 week, 6 weeks, 3 months, 6 months after surgery)

Prior to your discharge, we will set up an appointment for the 1-week follow-up and you will receive a confirmation phone call the day before. The other follow-ups will be arranged via telephone calls approximately 2 weeks before the assessment, with confirmation the day before. During the follow-up assessments, you will be asked to answer questionnaires regarding your pain, mood, memory, general wellness, symptom experience, wound healing, and satisfaction with your pain treatment. You will be asked to repeat functional assessments and tests to measure your sensitivity to pain. Blood will be taken to measure levels of cytokines, estrogen and progesterone. These assessments will take approximately 45 minutes to complete.

We will reimburse you for your travel or parking expenses for each visit to the hospital that might be needed for the study. You will be given a questionnaire package to complete and return in the mail. Postage will be provided and telephone reminders to return the questionnaires will be given at 2 and 4 weeks. If you live outside Toronto, or would prefer not to travel to UHN or not to have the Research Assistant visit you, telephone assessments consisting of the questionnaire package will be conducted.

One and two year assessment

We will telephone you one and two years after your surgery. You will be asked to complete several questionnaires about your memory, mood, pain history, medical history, activity levels and overall well-being. You will also be asked if you are taking any medications for pain or any other reason. We will coordinate a time to perform the functional assessments and tests to measure your sensitivity to pain around your follow-up medical appointment at UHN. After the physical testing, we will provide you with a questionnaire package that you may complete with the help of a research assistant or take home to complete. If you prefer to only complete the questionnaires, we will mail you the questionnaire package. The questionnaire package asks about your pain, how your pain impacts your life and your general health and wellbeing. Other parts of the questionnaire will ask you about personal information, such as marital status and personal relationships. It takes approximately 45 minutes to one hour to complete. We will provide you a stamped and addressed envelope so that you may return your completed questionnaire in the mail. We will telephone you in two and/or four weeks to remind you to mail your completed questionnaire. You are under no obligation to answer questions that you do not wish to answer, and you may feel free to take breaks as required.

Risks

Blood Tests

Blood sampling may be uncomfortable and cause some bruising. Some people may feel dizzy or light-headed when having blood samples taken.

Pain Sensitivity Testing

There may be a small amount of discomfort associated with testing your sensitivity to pain. None of these tests will cause any damage, and as soon as you report any pain the tests will be stopped.

Benefits

This study may not benefit you directly but it may potentially improve future pain management for patients undergoing surgical treatment for breast cancer.

Confidentiality

All information obtained during the study is completely confidential. You will be identified with a study number and initials only. No names or identifying information will be used in any publication or presentations.

Your health record will be looked at to evaluate any side effects of the treatment and to verify that we have accurate information regarding your health history and treatment. Certain sections of your chart (such as, anesthetic record and medication record) will be photocopied and included in your research chart for reference and evaluation. Any photocopies made will be confidential and any name or identifying information will be blacked out. In addition to the research team, your health record may be accessed by the Research Ethics Board for the purposes of verifying the information that is collected and ensuring that the study has been carried out properly.

Participation

Your participation in this study is voluntary. You can choose not to participate or you may withdraw at any time without affecting your medical care. You may be asked to withdraw from the study if at any time it is thought to be in your best interest.

Compensation

If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. The reasonable costs of such treatment will be covered by your health insurance for any injury or illness that is directly a result of participation in this trial. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities.

Questions

If you have any general questions about the study or suffer any side effects or other injuries during this study, please call Dr. Lucia Gagliese at 416-340-4296.

If you have any questions about your rights as a research participant, please call the University Health Network Research Ethics Board at 416-581-7849. They are not involved with the research project in any way and calling them will not affect your participation in the study.

Future Contact Consent

I voluntarily consent to be contacted for future research.

YES ☐

NO ☐

Consent

I have had the opportunity to discuss this study and my questions have been answered to my satisfaction. I consent to take part in the study with the understanding I may withdraw at any time without affecting my medical care. I have received a signed copy of this consent form. I voluntarily consent to participate in this study.

_____ _____ _____

Patient's Name (Please Print) Patient's Signature Date

I confirm that I have explained the nature and purpose of the study to the patient named above. I have answered all questions.

_____ _____ _____

Name of Person Obtaining Consent Signature Date