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The Effect of Constipation and Pain on the Psychoneurological Symptoms and Performance in Advanced Breast Cancer Women

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Abstract

Objective: Pain, depression, sleep disturbances, anxiety, and constipation are common symptoms in samples of women with breast cancer. These symptoms have a negative effect on performance status. In advanced breast cancer, pain and constipation were highly prevalent.

Similarly, depression, anxiety, and sleep disturbances were highly reported in the literature. Examining the effect of these symptoms on performance status in advanced breast cancer would help alleviate their negative effect on performance level and thereby improve patient's quality of life. This study sought to examine the individual effect of constipation and pain on performance when mediated by the psychoneurological symptoms (i.e., depression, anxiety, and sleep disturbances).

Methods: This study was a secondary analysis of a de-identified dataset that involved 86 women diagnosed with advanced breast cancer from a previous cross-sectional study.

Results: Logistic Regression showed that constipation has a highly significant effect on the psychoneurological symptoms. Indicating that severe constipation can lead patients to experience poor psychoneurological symptoms three times higher than non-constipated patients. The pain did not show a significant effect on performance when mediated by the psychoneurological symptoms. Although the effect of pain on performance was not statistically significant, study results indicated that severe pain increases the risk of having poor psychoneurological symptoms and poor performance status.

Conclusion: Constipation led to experience worse psychoneurological symptoms compared with patients who did not report constipation. The significant effect of Constipation on the psychoneurological symptoms highlights the importance of managing the effect of coexisting symptoms comprehensively to alleviate the effect of other correlated symptoms (e.g., pain and constipation).

Keywords: Constipation; Performance status; Breast cancer; Depression; Anxiety

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Introduction

Breast cancer is associated with multiple symptoms that might affect the patient's quality of life (QoL). Symptoms of breast cancer can negatively affect physical, psychological, and social wellbeing [1-7]. Pain, fatigue, depression, sleep disturbances, anxiety, nausea, vomiting, constipation, and other symptoms are reported frequently in women with breast cancer. Many of these symptoms are highly correlated and have been shown to have a negative effect on physical functioning

[8-11]. Pain is a highly prevalent and burdensome symptom in women diagnosed with breast cancer, as is constipation. Pain and constipation are associated with each other [10,12,13]. Constipation affects the frequency of evacuation and the stool component, leading to discomfort and psychological suffering during defecation. Passing a small and hard stool can be challenging and painful. The hard stool can also cause abdominal bloating and require strong straining to push the stool out of the body. The intensity of constipation varies from mild to severe based on the disease stage and treatment level. Severe



constipation can persist longer in advanced stages of cancer and lead to severe physical and psychological consequences. Most cancer patients who report constipation experience changes in activities of daily living (ADLs) and QoL [14].

Experts have suggested that pain and constipation are associated because the latter is a common side effect of opioid administration [14,15]. Opioids are used in cancer to treat moderate to severe pain [15]. They are associated with many side effects due to their other treatment actions. The most reported side effects are nausea, vomiting, drowsiness, and constipation. Opioids increase water absorption in the intestine, leading to hard fecal content that is difficult to evacuate [16].

Constipation may last over the opioid treatment period. In cancer patients, this means a prolonged and chronic constipation experience that could lead to serious bowel obstruction and other life-threatening complications.

Treating constipation early can help prevent serious complications. Pharmacologic (e.g., laxatives) and non-pharmacologic interventions (e.g., dietary fiber and abdominal massage) often relieve complications related to constipation. Late or untreated constipation leads to severe constipation that needs to be treated with high doses or more than one kind of laxative, which in turn can cause severe diarrhea; high doses and multiple laxatives may not result in any changes in the severity of constipation. Starting a planned comprehensive treatment regimen for cancer symptoms can help prevent serious complications and lead to better outcomes.

Problem Statement

Constipation impacts multiple dimensions of the patient's life, including physical, social, financial, and psychological aspects. The negative impact of constipation can influence the patient and their family, and it is considered a highly burdensome symptom. Constipation associated with pain has been found to produce a more negative impact on QoL [17]. Constipation can impair physical functioning and lead to an economic burden for both patient and family. Chronic constipation can also lead to depression [18].

Dhingra L, et al. (2013) found that patients who experienced opioid-induced constipation or diet-related constipation reported depression and anxiety [19]. Constipation was also associated with negative psychological status and poor levels of ADLs. Although both men and women are susceptible to constipation, women have been found to have a higher risk for severe constipation due to changes in psychological status that might lead to changes in appetite and physical activity [20-22].

Addressing symptom levels and managing them appropriately can alleviate the burden and promote wellbeing. Constipation level can be controlled by addressing symptoms early and managing them using appropriate comprehensive modalities. Management of cancer symptoms should focus on related symptoms that might cause the increasing intensity of other symptoms (e.g., managing severe pain with opioids leading to constipation). Therefore, managing correlated cancer symptoms in groups using different modalities can enhance QoL and physical functioning.

The effect of constipation on advanced breast cancer patients' psychoneurological symptoms and performance status when mediated by psychoneurological symptoms has not been established. Therefore, the purpose of this study was to examine the effects of pain and constipation as individual symptoms on psychoneurological

symptoms and performance status. Addressing both symptoms' effects on psychological outcomes was intended to facilitate the holistic assessment of the successful management of constipation.

Purpose

This study answers two research questions. Among women with advanced breast cancer:

- What is the effect of constipation on psychoneurological symptoms (depression, anxiety, and sleep disturbances) and performance status when mediated by the psychoneurological symptoms?
- What is the effect of pain on psychoneurological symptoms (depression, anxiety, and sleep disturbances) and performance status when mediated by the psychoneurological symptoms?

Methods

This study is a secondary analysis of a large 1,000 patient cross-sectional study at The Cleveland Clinic Foundation [13]. The secondary analysis used a subsample of 86 women diagnosed with advanced breast cancer from the parent study. A waiver of consent was obtained from the medical center Institutional Review Board (IRB) for the secondary analysis. This study tested the effects of pain and constipation individually on psychoneurological symptoms (depression, anxiety, and sleep disturbances) and performance status when mediated by one or more of the psychoneurological symptoms.

In the parent study, inpatients and outpatients were recruited if they had a diagnosis of incurable cancer and were referred to as palliative treatment. Patients were excluded if they were receiving active antitumor treatment. In this study, only women diagnosed with breast cancer were included. Participants were met by the physician or the primary care nurse to complete the study instruments. The parent study used two instruments. Cancer symptom intensity and frequency were measured using a 38-symptom checklist. Each patient was asked to rate their symptoms as present "1" or absent "0", then each symptom was rated as mild "1", moderate "2", or severe "3". Patient performance status was measured using the Eastern Oncology Cooperative Group (ECOG) scale. The instrument measures physical functioning on a single-item five-point Likert scale from "0: normal activity, no limitation" to "5: very sick, rarely out of bed". The ECOG scale has been used in samples of oncology patients [23] with interrater reliability of 0.59.

Analysis

This study analyzed the individual effects of pain and constipation on psychoneurological symptoms (depression, anxiety, and sleep disturbances) and performance status (such as "needs assistance" or "bedridden"). Logistic regression analysis measured the effects of pain and constipation on depression, anxiety, and sleep disturbances, as well as performance status, when mediated by the psychoneurological symptoms. To facilitate interpretation of the results, performance status was recoded into a binary variable. Performance status was labeled as "needs assistance" if it was rated as "some limitation in active work" or "requires considerable assistance" on the ECOG scale. The performance level was labeled as "bedridden" if it was rated as "spends most of the day in bed" or "very sick, rarely out of bed" on the ECOG scale.

Results

Eighty-six participants in this secondary analysis (n=86)



represented a subsample of the original dataset; they were diagnosed with an incurable stage of breast cancer and had been referred by their attending physician to a palliative medicine program. Participants were between 30 and 92 years old (mean=61.5, SD=12.7). All study participants showed a deviation of their performance level from normal. Thirty-one participants (36.1%) reported “needs assistance”, and 55 (63.9%) reported “bedridden”.

The individual effects of both pain and constipation on performance status (“needs assistance” and “bedridden”), when mediated by one or more of the psychoneurological symptoms (depression, anxiety, and sleep disturbances) are presented in (Table 1).

The first research question examines the effect of constipation on psychoneurological symptoms and performance status when mediated by the psychoneurological symptoms. The OR of the effect of constipation on performance status, when mediated by psychoneurological symptoms was not significant at the 90% CI (OR=1.1, CI=0.51-2.2), indicating that constipation had no significant effect on performance function (Table 1). However, constipation showed a significant effect on the psychoneurological symptoms (Table 2). Women who had moderate to severe constipation were three times more likely to have worse psychoneurological symptoms (OR=3, CI=1.18-7.62).

The second research question examines the effect of pain on psychoneurological symptoms and performance status when mediated by the psychoneurological symptoms. To confirm the effect of pain severity on performance status, the model of having pain, and at least one of the psychoneurological symptoms, was tested using

Table 1: Logistic regression model, mediation model of psychoneurological symptoms on binary performance level (N=86).

Variables	Model 1 OR [90% CI]	Model 2 OR [90% CI]	Model 3 Adjusted OR [90% CI]
Constipation			
Constipation “absent”			
Constipation “present”	1.2 [0.61 - 2.4]	-	1.1 [0.51 - 2.2]
Psychoneurological Symptoms			
Psychoneurological Symptoms (absent)			
Psychoneurological Symptoms (present)	-	1.6 [0.7 - 3.6]	1.5 [0.66 - 3.6]

Table 2: Logistic regression model for the psychoneurological symptoms (N=86).

Variables	Model 4 OR [90% CI]
Constipation	
Constipation “absent”	-
Constipation “present”	3 [1.18 - 7.62]*
Pain	
Pain “absent”	-
Pain “present”	1.56 [0.66 - 3.69]

Table 3: Logistic regression model, mediation model of psychoneurological symptoms on binary performance level (N=86).

Variables	Model 1 OR [90% CI]	Model 2 OR [90% CI]	Model 3 Adjusted OR [90% CI]
Pain			
Pain “absent”			
Pain “present”	1.5 [0.57 - 2.33]	-	1.06 [0.52 - 2.17]
Psychoneurological Symptoms			
Psychoneurological Symptoms (absent)			
Psychoneurological Symptoms (present)	-	1.6 [0.7 - 3.6]	1.5 [0.66 - 3.60]

logistic regression. The ORs showed that participants who had severe pain were 50% more likely to be bedridden (OR=1.5, CI=0.66-3.60) (Table 3). Testing the effect of pain on performance when mediated by psychoneurological symptoms showed no significant effect on performance status (OR=1.06, CI=0.52-2.17). The OR indicated that having moderate to severe pain increased the chance of having poorer performance status by 6%. The OR indicated that having severe pain increased the risk of having psychoneurological symptoms by 56%. However, this effect was not statistically significant (OR=1.56, CI=0.66-3.69) (Table 2).

Discussion

This study examined the effect of pain and constipation on psychoneurological symptoms (depression, anxiety, and sleep disturbances). A subset of 86 participants from a larger parent study was used in the secondary analysis [13]. Findings revealed that constipation significantly increased the risk of having at least one of the psychoneurological symptoms. No significant differences existed in the OR of the effect of pain on performance status. The OR of pain revealed no significant effect on having at least one of the psychoneurological symptoms.

Constipation is a stressful and burdensome symptom that negatively affects psychological and physical functioning. It can be related to multiple influencing factors, which may worsen the patient’s experience of the disease and its treatment. In this study, women diagnosed with advanced breast cancer who experienced constipation were three times more likely to have depression, anxiety, or sleep disturbances, indicating that constipation is negatively related to the psychoneurological status of cancer patients. Previous literature supports the relationship of constipation with QoL and psychological status among cancer patients, compared with patients diagnosed with other health issues [17]. The relationship between constipation and QoL was greater among patients who reported pain, which may be explained using constipation-producing analgesics. Constipation severity also influenced activity level and experience of other symptoms among non-cancer patients receiving opioids for the management of pain [24].

Palliative care of cancer patients whose antitumor cancer regimen is no longer effective is crucial to maintain QoL. Long-term pain management is associated with higher constipation levels, which can influence different aspects of psychological, physical, and social wellbeing [21,25]. Findings of one study Koloski NA, et al. (2013) showed that women diagnosed with cancer who had constipation experienced higher levels of depression and mortality, and poorer QoL [26]. Constipation has also been considered a possible cause of anxiety and depression among cancer patients, and this can affect their ability to participate meaningfully in ADL [19].

In this study, the findings did not show a significant effect of pain on psychoneurological symptoms, nor did pain have a significant effect



on performance status. This could be attributed to the differences in the severity level of the psychoneurological symptoms reported in this study compared to previous studies. For example, Kurtz et al. (2001) measured depressive symptomatology using the Center for Epidemiology Studies Depression Scale (CES-D), which has documented, well-established psychometric properties [27]. Of the 420 patients, 24% reported a score of 16 or higher on the CES-D scale, with a mean of 10.7. Given that the cutoff point for diagnosing depression using the CES-D scale is 16, these findings show relatively high scores on psychological symptoms [28].

The results also show that the high severity level of reported symptoms is associated with lower physical functioning levels. In this study, the pairwise correlation between physical functioning deficit and depressive symptomatology was 0.162 but was 0.510 with symptom severity. This could indicate that the severity level, rather than the prevalence of depressive symptoms, had the greatest effect on performance status.

In the current study, 43% of the 86 patients reported depression as “absent”, 11% “mild”, and 29% “moderate” or “severe”, while 17% of the sample reported the presence of depression but did not rate its severity. Of the same group, 54% reported anxiety as “absent”, 10% “mild”, and 13% “moderate” or “severe”, while 23% of the patients reported anxiety as present but was not rated. These percentages show that the level of psychological symptoms varied and was either not rated by the study participants or not severe. This might have affected the strength of the association between psychological symptoms and performance status.

Depression and anxiety are the two most common psychological symptoms experienced by patients diagnosed with cancer [13,29-33]. The association between individual psychoneurological symptoms and performance status has been reported in prior research studies. The findings in this study failed to support those of previous studies. For instance, Hong J, et al. (2013) reported that, among 93 participants with advanced nasopharyngeal cancer, anxiety had the greatest effect on performance status [34]. In the current study, only five participants (5.8%) reported mild anxiety, six (7%) reported moderate anxiety, and 26 (30%) reported anxiety but did not rate its severity; no participants reported severe anxiety. Likewise, participants’ reports of depression in this study ranged among mild (12 [14%]), moderate (12 [14%]), and severe (five [5.8%]); 18 participants (20%) reported depression but did not rate the severity. Therefore, although anxiety and depression were prevalent in this sample, the level of severity was low, and many participants did not rate their anxiety and depression even when present, which might have influenced the results.

The study has some limitations. A considerable percentage of participants did not rate the severity of certain symptoms listed on the 38-symptom checklist. The percentage of participants reporting the presence of symptoms, but not rating their severity level, was 30.2% for anxiety, 26.7% for constipation, 20.9% for depression, 18.6% for sleep disturbances, and 14% for pain.

Perhaps the use of the long symptom checklist with patients in advanced stages of breast cancer posed a degree of burden that led participants to identify symptoms but not rate them. The burdensome assessment of 38 symptoms listed on the checklist was addressed by Homsj J, et al. (2006), who commented that some of the symptoms in the checklist might have been volunteered by participants during an interview, thereby influencing the ability to rate all symptoms for severity [35]. The lack of data related to demographic variables (e.g., race, socioeconomic status) in this study limited the ability to explore

the effect of these factors on the tested relationships.

Conclusion

This study examined the effects of pain and constipation. Pain showed a negative effect on the psychoneurological symptoms and performance status of women diagnosed with advanced breast cancer. Constipation was associated with worse psychoneurological symptoms. The significant effect of constipation on psychoneurological symptoms highlights the importance of managing constipation in women with advanced breast cancer.

References

- Chen ML, Lin CC (2007) Cancer symptom clusters: a validation study. *J Pain Symptom Manage* 34: 590-599. <https://doi.org/10.1016/j.jpainsymman.2007.01.008>
- Dodd MJ, Miaskowski C, Paul SM (2001) Symptom clusters and their effect on the functional status of patients with cancer. *Oncol Nurs Forum* 28: 465-470.
- Given B, Given C, Azzouz F, Stommel M (2001) Physical functioning of elderly cancer patients prior to diagnosis and following initial treatment. *Nurs Res* 50: 222-232. <https://doi.org/10.1097/00006199-200107000-00006>
- Gift AG, Jablonski A, Stommel M, Given CW (2004) Symptom clusters in elderly patients with lung cancer. *Oncol Nurs Forum* 31: 202-212. <https://doi.org/10.1188/04.ONF.203-212>
- Kim HJ, McGuire DB, Tulman L, Barsevick AM (2005) Symptom clusters: concept analysis and clinical implications for cancer nursing. *Canc Nurs* 28: 270-282. <https://doi.org/10.1097/00002820-200507000-00005>
- Suwisith N, Hanucharunkul S, Dodd M, Vorapongsathorn T, Pongthavorakamol K, et al. (2008) Symptom clusters and functional status of women with breast cancer. *Thai J Nurs* 12:153-165.
- So WK, Marsh G, Ling WM, Leung FY, Lo JC, et al. (2009) The symptom cluster of fatigue, pain, anxiety, and depression and the effect on the quality of life of women receiving treatment for breast cancer: a multicenter study. *Oncol Nurs Forum* 36: E205-E214.
- Miaskowski C, Aouizerat BE (2007) Is there a biological basis for the clustering of symptoms? *Semin Oncol Nurs* 23: 99-105. <https://doi.org/10.1016/j.soncn.2007.01.008>
- Beck SL, Dudley WN, Barsevick A (2005) Pain, sleep disturbance, and fatigue in patients with cancer: using a mediation model to test a symptom cluster. *Oncol Nurs Forum* 32: 542. <https://doi.org/10.1188/04.onf.e48-e55>
- Kirkova J, Aktas A, Walsh D, Rybicki L, Davis MP (2010) Consistency of symptom clusters in advanced cancer. *Am J Hosp Palliat Care* 27: 342-346. <https://doi.org/10.1177/1049909110369869>
- Laird BJ, Scott AC, Colvin LA, McKeon AL, Murray GD, et al. (2011) Pain, depression, and fatigue as a symptom cluster in advanced cancer. *J Pain Symptom Manage* 42: 1-11. <https://doi.org/10.1016/j.jpainsymman.2010.10.261>
- Cleeland CS, Bennett GJ, Dantzer R, Dougherty PM, Dunn AJ, et al. (2003) Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. *Cancer* 97: 2919-2925. <https://doi.org/10.1002/cncr.11382>
- Walsh D, Rybicki L (2006) Symptom clustering in advanced cancer. *Support Care Cancer* 14: 831-836. <https://doi.org/10.1007/s00520-005-0899-z>
- Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, et al. (2009) The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). *Pain Med* 10: 35-42. <https://doi.org/10.1111/j.1526-4637.2008.00495.x>
- Droney J, Ross J, Gretton S, Welsh K, Sato H, et al. (2008) Constipation in cancer patients on morphine. *Support Care Cancer* 16: 453-459. <https://doi.org/10.1007/s00520-007-0373-1>
- Panchal SJ, Müller-Schwefe P, Wurzelmann JI (2007) Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *Int J Clin Pract* 61: 1181-1187. <https://doi.org/10.1111/j.1742-1241.2007.01415.x>
- Strömberg AS, Niemann CU, Tange UB, Farholt H, Sonne NM, et al. (2014) Quality of life and symptoms in patients with malignant diseases admitted to a comprehensive cancer centre. *Support Care Cancer* 22: 1843-1849. <https://doi.org/10.1007/s00520-014-2149-8>



18. Delgado-Guay MO, Kim YJ, Shin SH, Chisholm G, Williams J, et al. (2015) Avoidable and unavoidable visits to the emergency department among patients with advanced cancer receiving outpatient palliative care. *J Pain Symptom Manage* 49: 497-504. <https://doi.org/10.1016/j.jpainsymman.2014.07.007>
19. Dhingra L, Shuk E, Grossman B, Strada A, Wald E, et al. (2013) A qualitative study to explore psychological distress and illness burden associated with opioid-induced constipation in cancer patients with advanced disease. *Palliat Med* 27: 447-456. <https://doi.org/10.1177/0269216312450358>
20. Rajput M, Saini SK (2014) Prevalence of constipation among the general population: a community-based survey from India. *Gastroenterol Nurs* 37: 425-429. <https://doi.org/10.1097/SGA.0000000000000074>
21. Ferrell BR, Coyle N, Paice J (2014) Oxford textbook of palliative nursing. Oxford University Press, United Kingdom.
22. Younes WO, Tawalbeh LI (2017) Bowel management: constipation among patients with cancer. *J Palliat Care Med* 7: 2-6. <https://doi.org/10.4172/2165-7386.1000310>
23. Conill C, Verger E, Salamero M (1990) Performance status assessment in cancer patients. *Cancer* 65: 1864-1866. [https://doi.org/10.1002/1097-0142\(19900415\)65:8<1864::AID-CNCR2820650832>3.0.CO;2-U](https://doi.org/10.1002/1097-0142(19900415)65:8<1864::AID-CNCR2820650832>3.0.CO;2-U)
24. LoCasale RJ, Datto CJ, Margolis MK, Tack J, Coyne KS (2015) The impact of opioid-induced constipation among chronic pain patients with sufficient laxative use. *Int J Clin Pract* 69: 1448-1456. <https://doi.org/10.1111/ijcp.12718>
25. Kyle G (2011) Managing constipation in adult patients. *Nurse Prescribing* 9: 482-490. <https://doi.org/10.12968/npre.2011.9.10.482>
26. Koloski NA, Jones M, Wai R, Gill RS, Byles J, et al. (2013) Impact of persistent constipation on health-related quality of life and mortality in older community-dwelling women. *Am J Gastroenterol* 108: 1152-1158. <https://doi.org/10.1038/ajg.2013.137>
27. Kurtz ME, Kurtz JC, Stommel M, Given CW, Given B (2001) Physical functioning and depression among older persons with cancer. *Cancer Pract* 9: 11-18. <https://doi.org/10.1111/j.1523-5394.2001.91004.pp.x>
28. Radloff LS (1977) The CES-D: a self-report symptom scale to detect depression in the general population. *Appl Psychol Measur* 3: 385-401. <https://doi.org/10.1177/014662167700100306>
29. Chen E, Nguyen J, Khan L, Zhang L, Cramarossa G, T, et al. (2012) Symptom clusters in patients with advanced cancer: a reanalysis comparing different statistical methods. *J Pain Symptom Manage* 44: 23-32. <https://doi.org/10.1016/j.jpainsymman.2011.07.011>
30. Cheung WY, Le LW, Zimmermann C (2009) Symptom clusters in patients with advanced cancers. *Support Care Cancer* 17: 1223-1230. <https://doi.org/10.1007/s00520-009-0577-7>
31. Fan G, Hadi S, Chow E (2007) Symptom clusters in patients with advanced-stage cancer referred for palliative radiation therapy in an outpatient setting. *Support Cancer Ther* 4: 157-162. <https://doi.org/10.3816/SCT.2007.n.010>
32. Jiménez A, Madero R, Alonso A, Martínez-Marín, V, Vilches Y, et al. (2011) Symptom clusters in advanced cancer. *J Pain Symptom Manage*, 42: 24-31. <https://doi.org/10.1016/j.jpainsymman.2010.10.266>
33. Kirkova J, Rybicki L, Walsh D, Aktas A, Davis MP, et al. (2011) The relationship between symptom prevalence and severity and cancer primary site in 796 patients with advanced cancer. *Am J Hosp Palliat Care* 28: 350-355. <https://doi.org/10.1177/1049909110391464>
34. Hong J, Tian J, Zhang W, Pan J, Chen Y, et al. (2013) Patient characteristics as indicators for poor quality of life after radiotherapy in advanced nasopharyngeal cancer. *Head Neck Oncol* 5: 17.
35. Homsí J, Walsh D, Rivera N, Rybicki LA, Nelson KA, et al. (2006) Symptom evaluation in palliative medicine: patient report vs systematic assessment. *Support Care Cancer* 14: 444. <https://doi.org/10.1007/s00520-005-0009-2>