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Revisiting the cluster of symptoms: a mediation analysis between Pain, Anxiety, Depression and Fatigue

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Title Page

Revisiting the cluster of symptoms: a mediation analysis between Pain, Anxiety, Depression and Fatigue

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Abstract

Objective

Cancer treatment is a particularly stressful period for the patient. The reasons vary and include fear of treatment outcome as well as treatment induced side-effects. The patient frequently experiences simultaneously various somatic and psychological side-effects resulting in a diminishing of the patient's health related quality of life-HRQoL. The study provides evidence on the co-occurrence and interrelations between pain, anxiety, depression and fatigue in patients diagnosed with breast and prostate cancer.

Design

This was a Randomised Control Trial designed to test the effectiveness of Guided Imagery and Progressive Muscle Relaxation on pain, fatigue, anxiety and depression. Non-parametric bootstrapping analyses were used to test the meditational model of Anxiety, Fatigue and Depression as parallel mediators of the relationship between Pain and HRQoL. The ClinicalTrials.gov NCT01275872

Setting

The study was undertaken at the home setting

Participants

In total 208 patients were included in the study (assigned equally in two groups), referred at the out-patient clinics of the three participating cancer care centres.

Results

The three mediators fully mediate the relationship between Pain and HRQoL ($IE_{overall}$=-0.3839, 95% C.I.: LL=-0.5073, UL=-0.2825) indicating that patients with increased Pain are

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more likely to have higher levels of Anxiety, Fatigue and Depression. Gender significantly moderated the mediational effect of Fatigue (IMM=-0.2867 SE=0.1526, LL=-0.6127, UL=-0.0226) but did not moderate mediational effect of Anxiety (IMM=-0.0709, SE=0.1414, LL=-0.3459, UL=+0.2089). The results show that the three mediators in a serial causal order fully mediate the relationship between Pain and HRQoL ($IE_{overall}$=-0.384, 95% C.I.: LL=-0.51, UL=-0.284) and the ratio of the overall indirect effect to the total effect, is 0.8315 (95% CI: LL=0.5683, UL=1.1718).

Conclusion

This work provides evidence that targeting fatigue, anxiety and depression may have a meaningful effect on pain as a related symptom and potentially have a positive impact on HRQoL of patients with breast cancer and prostate cancer.

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Strengths and Limitations of the Study

- The study provided evidence that targeting fatigue, anxiety and depression may have a meaningful effect on pain
- The study provided evidence on the direct and indirect effects of this symptom cluster on the person's HRQoL.
- The moderated mediation analysis showed that Gender significantly moderated the mediational effect of Fatigue but did not moderate mediational effect of Anxiety.

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Introduction

Cancer treatments and cancer itself are a source of many symptoms and side-effects [1-2] It is reported that on average cancer patients experience 11 to13 concurrent symptoms, whilst for patients with advanced disease the number can be even greater [3]. Often these symptoms are related to each other, called symptom clusters (CSs) or symptom constellations[3]. Dodd et al[4-6] defined symptom cluster as 3 concurrent and related symptoms that may or may not have a common etiology. However, the authors suggested that a cluster can be composed of just 2 or more symptoms that form a stable group[3]. Symptoms can be related through a common mechanism or etiology, by sharing common variance, or by producing different outcomes than individual symptoms. The impact of these clusters can be accumulative and debilating for the patient and far more serious and persistent than single symptoms. They can affect the patient's overall HRQoL [7] and significantly affect the patient's sense of wellbeing and his or her physical and social functions [8]. A number of studies have tried to record the most common clusters in various cancer types[4,9], however due to the lack of agreement about a robust, clinically relevant definition of SCs, their results should be interpreted with caution. Although the groups of symptoms that tended to cluster were identified, there is limited consistency in the way in which these SCs and their associated variables were identified[1]. Preceding studies, again by drawing on the weaknesses of the clinical definition of a SC, they provide limited information towards understanding the way (or ways) the symptoms are actually correlated to each other or to other variables (i.e. HRQoL). According to the definition by Dodd et al[4] for example, a cluster of pain, fatigue and insomnia is presented as a legitimate one. However the authors supported that pain leads to fatigue and in turn insomnia and this is a rather linear representation that does not explain if these symptoms can possibly have an alternative way of interaction other than the one suggested. The same problem appears with the other SCs that have been identified so far in the literature

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leaving a gap to the best understanding of this phenomenon but most importantly to the way it can be best clinically managed. When interventions are directed to ameliorate a particular symptom within a cluster, other symptoms within the cluster may be relieved. However this evidence is not available to the best of our knowledge in the relevant literature. As a result, current practice is driven based on *a priori* assumptions about the relationships among symptoms resulting in targeting the "dominant" symptom. In the previous example, pain would have been identified as a "dominant" symptom and therefore secondary attention is attributed to any other symptom that co-occurs. These *a priori* assumptions are however not based on scientific evidence but rather have been established on clinical experience. However, a symptom cluster experienced by the patient creates a complex condition where pain is rarely reported as a single symptom, but as a distressing symptom is reported and addressed in a timely manner. However, the lack of knowledge in the ways symptoms might correlate to each other and with other variables, the question remains whether the dominant symptom in these situations is indeed pain. The question that also arises is whether there would be a clinical benefit if for example pain and fatigue are correlated and interventions were specifically designed to target both symptoms. The researchers so far had hypothesised that it is pain and this has become the common practice dominating the current clinical management of this specific SC.

Aim

The aim of this study was to provide evidence on the co-occurrence of and interrelations between symptoms occurring as part of a cluster in two groups of patients diagnosed with breast and prostate cancer.

Methods

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The data came from a Randomised Control Trial (NCT01275872) designed to test the effectiveness of Guided Imagery (GI) and Progressive Muscle Relaxation (PMR) on a cluster of symptoms reported by patients diagnosed with breast or prostate cancer when receiving chemotherapy[10]. This study was done in compliance with the Declaration of Helsinki and the protocol was approved by the Cyprus National Bioethics Committee (CNBC/EP/2010/06). The patients reported symptoms such as fatigue, pain, nausea, vomiting and retching, anxiety and depression. Assessments included a 10-point numeric scale for pain, the Cancer Fatigue Scale (CFS)[11], Revised Rhodes index of nausea, vomiting and retching (INVR)[12] the Zung self-rating anxiety scale SAS[13] and the Beck Depression Inventory-II[14]. As with the majority of studies that explore symptom and symptom management, Quality of Life is a frequently reported outcome that has been used to demonstrate the negative impact of symptoms but also to reflect on the effectiveness of symptom management strategies. HRQoL was included in the study due to the consistent evidence in the literature that the cluster of symptoms is associated to poor levels of quality of life in patients diagnosed with cancer[15,16, 7]. Therefore, Health Related Quality of Life (HRQoL) has also being introduced in this study as a variable that can be correlated to the studied symptoms. The HRQoL of the patients was assessed with the EORTC QLQ-C30 module in addition to the module BR23 for breast cancer patients and the module PR25 for prostate cancer patients.

As the rationale for this study was to test the correlations between symptoms identified as clusters, only the baseline (T0) measurements from both groups (intervention and control group) were included in the analysis. Based on predetermined criteria, 208 patients were included in the study. The sample included 104 female breast cancer patients (52 in control group + 52 in intervention group) and 104 prostate cancer patients (52 in control + 52 in intervention). The study was complioant to the Declaration of Helsinki and the protocol was

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approved by the Cyprus National BioEthics Committee (ID CNBC/EP/2010/06). All participants signed an informed consent prior to their inclusion in the study. A detail presentation of the study's methodology is presented elsewhere[17].

Statistical analysis

Non-parametric bootstrapping analyses[18] were deployed to test the meditational model of Anxiety, Fatigue and Depression as parallel mediators of the relationship between Pain and HRQoL. The nausea, vomiting and retching were excluded from the analyses as these were not found to correlate with the other symptoms. In these analyses, mediation is significant if the 95% Bias Corrected and accelerated confidence intervals (Lower Limit - LL), Upper Limit (UL) for the indirect effect do not include 0[8, 18]. Moreover, separated regression analyses were deployed to explore the statistical association of Gender and Age of the patient with the HRQoL.

Three mediation models are hypothesized and explored. The first model is a gender adjusted parallel mediation model of indirect effect of Pain to HRQoL through Anxiety, Fatigue and Depression. The second model is a moderated mediation model where the indirect effects are explored on each gender (conditional indirect effects). The third model assumes a serial causal chain of the three mediators (serial mediation). Six different causal chains were explored in this model.

All involved variables in the analyses were standardized (z scores) before running the analyses, hence standardized coefficients are reported for the Total, Direct and Indirect effects.

Analysis was performed by utilising the PROCESS function v.2.16.1 in SPSS v.21. The model 4 (model as a parameter in the PROCESS function) was used for the parallel

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mediation model, model 15 (moderated mediation) for the second mediation model and model 6 for the serial mediation models[19].

Model fit is also reported using the following: a chi-square (df, a comparative fit index (CFI)>0.90 and a root mean square error approximation (RMSEA) of <0.10. The fit indices were derived using the package *lavaan* in R[20].

Results

The correlation analysis shows that HRQoL is negatively associated with Pain (r=-0.462), Fatigue (r=-0.601), Anxiety (r=-0.595) and Depression (r=-0.510) indicating that lower quality of life is associated with higher levels of the psychological aspects as well as Pain. Furthermore, Pain is positively correlated with all psychological aspects and negatively correlated with HRQoL (Table 1).

Covariates

Age was not found to be statistically associated with the level of HRQoL either on the Total Effects model (b=-1.13 p=0.27, Predictors of HRQoL: Pain, Sex, Age) or on the Direct Effect model (b=-0.9903 p=0.2866, Predictors to HRQoL: Anxiety, Fatigue, Depression, Pain, Gender, Age).

Gender was found to be statistically associated with the HRQoL in the Total Effects model (b=-7.2972 p=0.0143) indicating that female patients experienced lower quality of life compared to male patients. Therefore, gender which in this study also reflects the type of cancer, is included in the mediation models as a statistical control variable.

Parallel mediation model

Results based on 5000 bootstrapped samples indicated that, controlling for the gender, whilst the total effect of Pain on HRQoL was significant (β_{total}=-0.4616, SE=0.0612, p<0.001), the

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direct effect was not (β_{direct}=-.0778, SE=0.0685, p=0.2576) and indirect effects (IE) are present (Figure 1).

Overall, the three mediators fully mediate the relationship between Pain and HRQoL ($IE_{overall}$=-0.3839, 95% C.I.: LL=-0.5073, UL=-0.2825) indicating that patients with increased Pain are more likely to have higher levels of Anxiety, Fatigue and Depression. Patients through the experience of high levels of Anxiety, Fatigue and Depression, are more likely to report lower levels of Quality of Life.

Two out of the three mediators were found to significantly contribute to the overall indirect effect. Specifically, there is as statistically significant indirect effect of Pain to HRQoL though Anxiety ($IE_{anxiety}$=-0.1378, 95% C.I.: LL=-0.2615, UL=-0.0395), such that participants who indicated high levels of Pain were more likely to feel Anxiety, and through high levels of Anxiety, more likely to report lower levels of HRQoL. In addition, there is as statistically significant indirect effect of Pain to HRQoL though Fatigue ($IE_{fatigue}$=-0.1856, 95% C.I.: LL=-0.2716, UL=-0.1093), such that patients who indicated high levels of Pain were more likely to feel Fatigue, and through high levels of Fatigue, more likely to report reduced HRQoL. Depression does not mediate the relationship between Pain and HRQoL ($IE_{depression}$=-0.0605, 95% C.I.: LL=-0.1575, UL=+0.0289).

Specific indirect effect contrasts between the proposed mediators do not show statistically significant difference between the indirect effects of Anxiety and Fatigue (b=0.0478, 95% CI: LL=-0.260, UL=0.0822). The ratio of the overall indirect effect to the total effect, is 0.8315 (95% CI: LL=0.5683, UL=1.1718), while the ratio of the Anxiety and Fatigue indirect effects to the Total effect is 0.2985 (95% CI: LL=0.0758, UL=0.5711) and 0.4020 (LL=0.2230, UL=0.6317) respectively.

Moderated mediation model - Gender moderation

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The current analysis tests whether the indirect effect of Pain to HRQoL through Anxiety or Fatigue is moderated by Gender, i.e. whether the mediation effect observed earlier, is statistically significantly different in Males and Females.

A moderated mediation model is explored where Anxiety and Fatigue act as parallel mediators and Gender as a moderator (Figure 1) to the mediation. The proposed model is under model 15 of the PROCESS documentation[19] where the moderation effect takes place at the B-Path (Mediator to Dependent) and at the C- path (direct path: Independent to Dependent). Model 15 (moderation effect not included to the A-path), was chosen over Model 59 (moderation effect on all paths) since separate regression analysis for the interaction of Gender to the relationship of the Independent (Pain) to the Mediators (Anxiety and Fatigue) did not reach statistical significance. The slope of the line relating the indirect effect to the moderator is the "index of moderated mediation" (IMM)[20].The statistical significance of the IMM effect is assessed along with the conditional indirect effects across each gender.

Gender significantly moderated the mediational effect of Fatigue (IMM=-0.2867 SE=0.1526, LL=-0.6127, UL=-0.0226) but did not moderate mediational effect of Anxiety (IMM=-0.0709, SE=0.1414, LL=-0.3459, UL=+0.2089). This means that there is a meaningful difference in the magnitude of the conditional indirect effects of each gender in the mediation effect of Pain to HRQoL through Anxiety. Specifically, we observe that for Males the conditional indirect effect is trivial and not statistically significant (β=0.0746, SE=0.1474, LL=-0.1893, UL=+0.3853) but for Females the conditional indirect effect is stronger than Males' and statistically significant (β=-0.2121, SE=0.0434, LL=-0.307, UL=-0.1351) (Table 2). Fatigue is a significant mediator to the relationship between Pain and HRQoL for Females

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rather than Males. There is no meaningful difference in the mediating effect of Anxiety for the relationship between Pain and HRQoL between Males and Females.

Serial mediation model

Serial mediation hypothesizes a causal chain linking of the mediators (Anxiety, Fatigue, Depression), with a specified direction flow. For example, Pain, could increase Anxiety, which in turn increases Depression which could in turn increase Fatigue and thus decrease Quality of Life. (i.e., Pain->Anxiety->Depression-Fatigue->HRQoL).

The results show that the three mediators in a serial causal order (any order that is) ***fully mediate*** the relationship between Pain and HRQoL ($IE_{overall}$=-0.384, 95% C.I.: LL=-0.51, UL=-0.284) and the ratio of the overall indirect effect to the total effect, is 0.8315 (95% CI: LL=0.5683, UL=1.1718). The total indirect effect and the ratio to the total effect, both are the same as in the parallel mediation model explored earlier.

Since three mediators were used, six different causal order models were produced (Table 3). All six models were compared in terms of the significant path created by each different causal order of the mediators. SMM 1, SMM 2 and SMM 4 yielded only three significant indirect paths out of the 7 possible paths, whereas SMM 3, SMM 5 and SMM6 yielded 4, 5 and 6 significant paths respectively.

SMM 3, SMM 5 and SMM 6 yielded a significant indirect path involving all 3 mediators in a causal chain. The path *Pain->Depression->Anxiety->Fatigue->HRQoL* in SMM 3 yielded the highest ratio of indirect to total effect; 0.126 (95% C.I.: 0.056-0.248) among the three models (Table 3).

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The indirect paths involving *Fatigue* and *Depression* (one after the other and vice-versa) were statistically significant in 1 out of the 6 SMMs and specifically in SMM6.

The indirect paths involving *Anxiety* and *Depression* (one after the other and vice-versa) was statistically significant in 3 out of the 6 SMMs and specifically in SMM3, SMM5, and SMM6

The indirect paths involving *Fatigue* and *Anxiety* (one after the other and vice-versa) were statistically significant in all SMMs. This result means that increased Pain increases Fatigue (or Anxiety) which in turn increase Anxiety (or Fatigue) resulting in a decreased Quality of Life. The serial causal effect of these two mediators was found significant in any casual order of the mediators in place.

Figure 3 depicts the effects of the direct paths linking pain to each mediator and among mediators resulting from the SMM 6 in which all the direct and indirect effects are statistically significant. The positive signs (+ve) of the effects are indicative of the increased Anxiety, Fatigue and Depression that increased Pain causes. Moreover, it shows that increased levels of each mediator is associated with a positive effect (i.e. increase) in the levels of the mediator with a direct connection. All indirect paths from Pain to HRQoL are negative, showing the reduction in HRQoL levels through the increase in the levels of the mediators. The SMM 6 results show that the worst the Pain was the more it would contribute to Depression, higher depression resulted to higher Fatigue, higher Fatigue led to higher levels of Anxiety which in turn contributed to lower HRQoL.

Discussion

The aim of this study was to explore the correlations between symptoms that were reported by two cancer patient groups and HRQoL. We specifically aimed to demonstrate that pain,

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depression, fatigue, and anxiety co-occur as a symptom cluster over the course of breast cancer and prostate cancer treatment. Findings indicate that with the exception of nausea, vomiting and retching, the symptoms of pain, fatigue, anxiety and depression formed a common symptom cluster in both breast and prostate cancer patients. The findings also showed that HRQoL is negatively associated with pain, fatigue, anxiety and depression. This suggests that with these two groups of patients the symptoms consisting of the cluster need to be addressed collectively not only emphasizing on pain management but also focusing on depression, anxiety and fatigue. This provides a more comprehensive symptom management to the patient with also a positive effect on the HRQoL.

Parallel, serial and moderate mediation analyses yielded interesting results in relation to symptom correlations. Parallel mediation analysis showed that the three mediators (fatigue, anxiety, and depression) fully mediate the relationship between Pain and HRQoL. However, whilst Anxiety and Fatigue were found to significantly contribute to the overall indirect effect, Depression did not mediate the relationship between Pain and HRQoL. Although the data used for the analysis cannot support a definite model as these data were not longitudinal, however it does suggest that researchers and clinicians should consider these alternative correlations between symptoms and HRQoL. For example, gender significantly moderated the meditational effect of Fatigue but not Anxiety. Therefore, for Males (i.e. prostate cancer patients) conditional indirect effect is minimal but for Females (i.e. breast cancer patients) the effect is stronger and statistically significant. With the existence of many complex variable correlations being recorded in the literature in isolated symptom studies, these new findings suggest that conflicts in preceding studies may be resolved by the increased understanding of variable interaction in symptom clustering.

The exact underlying mechanisms by which symptoms correlate with each other are not to this date fully understood and this is an area that could contribute in the comprehensive

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management of symptom clusters through the development of effective multimodal interventions for breast and prostate cancer patients for use in the active treatment phase. A variety of non-pharmacological interventions have been proposed for treating pain, fatigue, depression and anxiety including exercise, psychosocial, cognitive behavioural, and nutritional[22-24]. However, most of these recommendations are proposed for use in single symptom management, perhaps with the exception of guided imagery and progressive muscle relaxation that its effectiveness was also tested in symptom cluster[17]. Further research is needed towards examining whether multimodal interventions can reduce pain and, in turn, reduce depression, fatigue and anxiety.

Clinical decision making in symptom management is traditionally driven by the type of the symptom rather than its impact on the patient or its correlations to other symptoms that might simultaneously be present. Preceding studies[25] consistently showed that emphasis is given on pain management rather than management of other symptoms such as fatigue or anxiety within a clinical situation where a symptom cluster manifests. The main problem with these patterns in symptom management is that despite the knowledge that symptoms co-exist; these are prioritised according to perceived importance. However, the correlation between the symptoms is purposively not taken into consideration including the likelihood that by treating for example Fatigue in breast cancer patients, the results of any pain management intervention might be fortified as well as the positive impact on HRQoL. On the same example, treating Fatigue in prostate cancer patients will most likely have no accumulating effect on the patient's responsiveness to pain management interventions. This example highlights that within the clinical setting such clinical decision making has also an impact on the cost-effectiveness of the symptom management interventions, as resources can be purposively allocated to other symptoms or variables that mediate pain and HRQoL to maximise clinical management.

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The study has some limitations. The main limitation is the small sample size; however, several statistically significant paths emerged and within-symptom paths were replicated across both study samples (i.e cancer type groups). The unavailability of longitudinal data limits the support of a definite model, which would demonstrate if the correlations between symptoms found in this study are stable over time. However, the fact that the patients in the study were all in the active treatment phase strengthens the generalisability of the results to patients with prostate and breast cancer during this phase.

The study demonstrated that pain, depression, fatigue, and anxiety tend to co-occur during the treatment phase, thus providing further evidence for this symptom cluster in two distinct samples of breast and prostate cancer patients. The study also showed the direct and indirect effects of this symptom cluster on the person's HRQoL. Parallel mediation analysis showed that the three mediators (fatigue, anxiety, and depression) fully mediate the relationship between Pain and HRQoL. Similarly, in a serial causal order, the three mediators fully mediate the relationship between Pain and HRQoL. The moderated mediation analysis showed that Gender significantly moderated the mediational effect of Fatigue but did not moderate mediational effect of Anxiety. There are explicit clinical implications of the study's findings that include assessment, prevention, and intervention for anxiety, depression, fatigue and pain related to breast and prostate cancer treatment. This work provides preliminary evidence that targeting fatigue, anxiety and depression may have a meaningful effect on pain as a related symptom and potentially have a positive impact on HRQoL of patients with breast cancer and prostate cancer.

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Data Statement

Data are available from the Cyprus University of Technology given that the Cyprus National BioEthics Committee will grant access to data for researchers who meet the criteria doe access to confidential data. Data requests can be sent to the corresponding author at andreas.charalambous@cut.ac.cy

Author Statement

The authors of this paper have directly participated in all the stages of its preparation. Authorship statement: AC conceived and designed the study, analyzed, interpreted the data and approved the final manuscript. MG prepared all the draft versions of the manuscript. YM, PK recruited the participants, interpreted the data and edited and approved the final version of the manuscript. AC, MG, EB collected the data. LP performed the statistical analysis and interpretation of the data. AC, MG, LP interpreted the data, edited and approved the final version of the manuscript. AC, LP were responsible for the financial support.

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Table 1: Pearson correlation coefficients between the variables

	Pain	Fatigue	Anxiety	Depression	HRQoL
Pain	1				
Fatigue	,567**	1			
Anxiety	,590**	,715**	1		
Depression	,541**	,565**	,735**	1	
HRQoL	-,462**	-,601**	-,595**	-,510**	1

** p<0.001

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Table 2: Conditional indirect effect(s) of PAIN on HRQoL at Gender and Index of Moderated Mediation

Mediators	Moderator (Gender)	β(SE)	95% Confidence Interval
Anxiety			
	Male	0.1324 (0.1314)	(-0.4076, 0.1138)
	Female	-0.2033 (0.0578) *	(-0.3315, -0.1026)
Fatigue			
	Male	0.0746 (0.1463)	(-0.2015, 0.3574)
	Female	-0.212 1(0.0436) *	(-0.3034, -0.1282)

Moderated Mediation Index

Mediator	β(SE)	95% Confidence Interval
Anxiety	-0.0709 (0.143)	(-0.3583, 0.2094)
Fatigue	-0.2867 (0.156) *	(-0.5996, -0.0057)

*p<0.05, Bias corrected bootstrapped Confidence Intervals, 5000 bootstrap samples. Statistically significant moderated mediation occurs only for Fatigue. Although there is a significant conditional indirect effect for Females through the mediator Anxiety, the difference between the conditional indirect effect for Males is not significantly different than that of the Females.

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Table 3: Standardised indirect effects and ratio of indirect to total effects for the paths on the serial mediation models.

	Indirect effects of Pain on HRQoL		Ratio of indirect to total effect	
	b (boot SE)	BC 95% CI [LB-UB] †	b (boot SE)	BC 95% CI [LB-UB] †
SMM1: PN -> AXT -> DEP -> FTG -> HRQoL				
PN -> AXT -> HRQoL	-0,138 (0,057)	(-0,268, -0,04)	0,299 (0,126)	(0,082, 0,581)
PN -> AXT -> DEP -> HRQoL	-0,042 (0,033)	(-0,109, 0,022)	0,091 (0,074)	(-0,049, 0,239)
PN -> AXT -> FTG -> HRQoL	-0,108 (0,032)	(-0,186, -0,057)	0,234 (0,077)	(0,114, 0,424)
PN -> AXT -> DEP -> FTG -> HRQoL	-0,004 (0,01)	(-0,028, 0,013)	0,009 (0,022)	(-0,029, 0,063)
PN -> DEP -> HRQoL	-0,018 (0,018)	(-0,069, 0,005)	0,04 (0,04)	(-0,012, 0,153)
PN -> DEP -> FTG -> HRQoL	-0,002 (0,005)	(-0,019, 0,005)	0,004 (0,011)	(-0,01, 0,041)
PN -> FTG -> HRQoL	-0,071 (0,024)	(-0,13, -0,033)	0,154 (0,056)	(0,07, 0,296)
SMM2: PN -> FTG -> AXT-DEP -> HRQoL				
PN -> FTG -> HRQoL	-0,186 (0,042)	(-0,272, -0,11)	0,299 (0,126)	(0,082, 0,581)
PN -> FTG -> AXT -> HRQoL	-0,074 (0,032)	(-0,146, -0,023)	0,244 (0,077)	(0,119, 0,427)
PN -> FTG -> DEP -> HRQoL	-0,002 (0,006)	(-0,022, 0,006)	0,088 (0,074)	(-0,047, 0,241)
PN -> FTG -> AXT -> DEP -> HRQoL	-0,022 (0,018)	(-0,063, 0,011)	0,003 (0,008)	(-0,007, 0,029)
PN -> AXT -> HRQoL	-0,064 (0,03)	(-0,141, -0,018)	0,158 (0,058)	(0,071, 0,304)
PN -> AXT -> DEP -> HRQoL	-0,019 (0,017)	(-0,062, 0,008)	0,002 (0,005)	(-0,004, 0,024)
PN -> DEP -> HRQoL	-0,018 (0,017)	(-0,067, 0,005)	0,038 (0,039)	(-0,012, 0,147)
SMM3: PN -> DEP>AXT -> FTG-- -> HRQoL				
PN -> DEP -> HRQoL	-0,061 (0,048)	(-0,156, 0,03)	0,131 (0,106)	(-0,072, 0,343)
PN -> DEP -> AXT -> HRQoL	-0,074 (0,031)	(-0,15, -0,021)	0,161 (0,07)	(0,044, 0,324)
PN -> DEP -> FTG -> HRQoL	-0,006 (0,015)	(-0,043, 0,018)	0,014 (0,032)	(-0,038, 0,094)
PN -> DEP -> AXT -> FTG -> HRQoL	-0,058 (0,019)	(-0,105, -0,028)	0,126 (0,047)	(0,057, 0,248)
PN -> AXT -> HRQoL	-0,064 (0,029)	(-0,138, -0,019)	0,138 (0,065)	(0,042, 0,306)
PN -> AXT -> FTG -> HRQoL	-0,05 (0,017)	(-0,094, -0,025)	0,108 (0,038)	(0,053, 0,212)
PN -> FTG -> HRQoL	-0,071 (0,024)	(-0,13 , -0,033)	0,154 (0,056)	(0,07 , 0,296)
SMM4: PN -> AXT -> FTG -> DEP> -> HRQoL				
PN -> AXT -> HRQoL	-0,138 (0,056)	(-0,262 , -0,04)	0,299 (0,125)	(0,076 , 0,578)
PN -> AXT -> FTG -> HRQoL	-0,113 (0,031)	(-0,187 , -0,061)	0,244 (0,076)	(0,122 , 0,426)
PN -> AXT -> DEP -> HRQoL	-0,041 (0,034)	(-0,115 , 0,02)	0,088 (0,075)	(-0,045 , 0,259)
PN -> AXT -> FTG -> DEP -> HRQoL	-0,001 (0,004)	(-0,013 , 0,003)	0,003 (0,008)	(-0,007 , 0,028)
PN -> FTG -> HRQoL	-0,073 (0,025)	(-0,131 , -0,031)	0,158 (0,058)	(0,065 , 0,299)
PN -> FTG -> DEP -> HRQoL	-0,001 (0,003)	(-0,011 , 0,002)	0,002 (0,006)	(-0,004 , 0,022)
PN -> DEP -> HRQoL	-0,018 (0,017)	(-0,067 , 0,005)	0,038 (0,039)	(-0,01 , 0,152)
SMM5: PN -> FTG -> DEP>AXT -> HRQoL				
PN -> FTG -> HRQoL	-0,186 (0,042)	(-0,272 , -0,11)	0,402 (0,103)	(0,223 , 0,632)
PN -> FTG -> DEP -> HRQoL	-0,024 (0,019)	(-0,064 , 0,011)	0,052 (0,042)	(-0,023 , 0,146)
PN -> FTG -> AXT -> HRQoL	-0,052 (0,023)	(-0,106 , -0,016)	0,112 (0,051)	(0,031 , 0,23)
PN -> FTG -> DEP -> AXT -> HRQoL	-0,022 (0,011)	(-0,05 , -0,007)	0,049 (0,024)	(0,015 , 0,11)
PN -> DEP -> HRQoL	-0,036 (0,031)	(-0,106 , 0,016)	0,079 (0,069)	(-0,034 , 0,238)
PN -> DEP -> AXT -> HRQoL	-0,034 (0,015)	(-0,07 , -0,01)	0,073 (0,034)	(0,021 , 0,156)
PN -> AXT -> HRQoL	-0,03 (0,019)	(-0,082 , -0,004)	0,065 (0,042)	(0,008 , 0,181)
SMM6: PN -> DEP>FTG -> AXT -> HRQoL				

PN -> DEP -> HRQoL	-0,061 (0,048)	(-0,158 , 0,029)	0,131 (0,107)	(-0,065 , 0,355)
PN -> DEP -> FTG -> HRQoL	-0,065 (0,023)	(-0,12 , -0,03)	0,14 (0,054)	(0,062 , 0,283)
PN -> DEP -> AXT -> HRQoL	-0,056 (0,023)	(-0,111 , -0,017)	0,122 (0,053)	(0,033 , 0,245)
PN -> DEP -> FTG -> AXT -> HRQoL	-0,018 (0,009)	(-0,043 , -0,006)	0,039 (0,021)	(0,011 , 0,096)
PN -> FTG -> HRQoL	-0,121 (0,031)	(-0,192 , -0,07)	0,262 (0,073)	(0,146 , 0,44)
PN -> FTG -> AXT -> HRQoL	-0,034 (0,016)	(-0,073 , -0,011)	0,073 (0,035)	(0,021 , 0,16)
PN -> AXT -> HRQoL	-0,03 (0,019)	(-0,082 , -0,004)	0,065 (0,042)	(0,008 , 0,181)

Notes: Table shows standardized indirect effects with bootstrapped standard errors; Paths in bold indicate statistically significant indirect effects; PN=Pain, DEP=Depression, AXT=Anxiety, FTG=Fatigue, HRQoL = Quality of Life; $^{\int}$ Bias Corrected 95% confidence intervals; SMM=Serial Mediation Model

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Figure 1. Parallel Mediation Model (n=212). Indirect effects of Pain on Global HRQoL through Anxiety, Fatigue and Depression. Note: Model is controlled for the gender. Standardized effects are presented. The effects on the direct path from Pain to Global HRQoL depict the Direct effect and the (Total effect). *p < .05, ** p < .01, ***p < .001

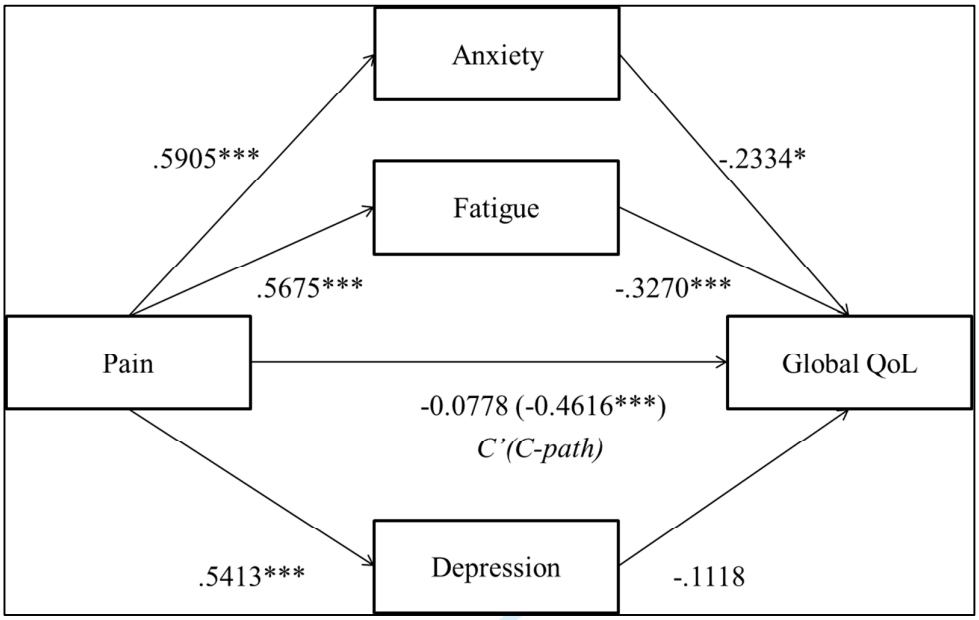

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Figure 2. Moderated Mediation Model (n=212). Conditional Indirect effects on Gender (Female coded as 1 and Males as 0) of Pain on Global HRQoL through Depression. Note: Standardized effects are presented. The effects on the direct path from Pain to Global HRQoL depict the Conditional Direct Effects for each gender as well as the unconditional direct effect C' path (Total effect C-path). The effects of the moderator Gender to the paths represent the interaction slopes. Effects on the B-paths from the mediators to HRQoL represent the simple slopes. *p < .05, ** p < .01, ***p < .001

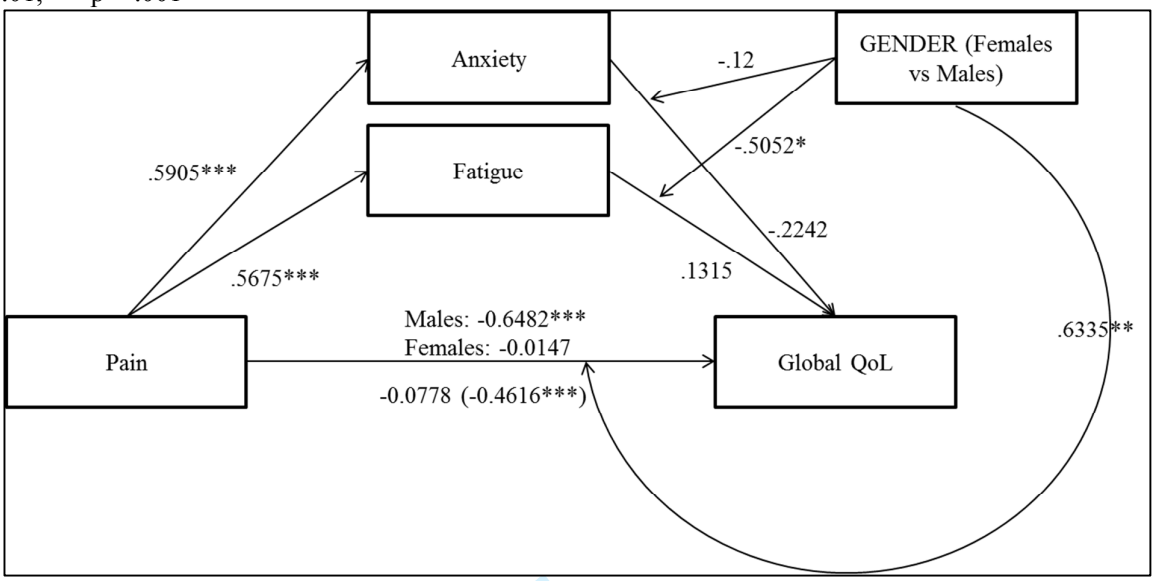

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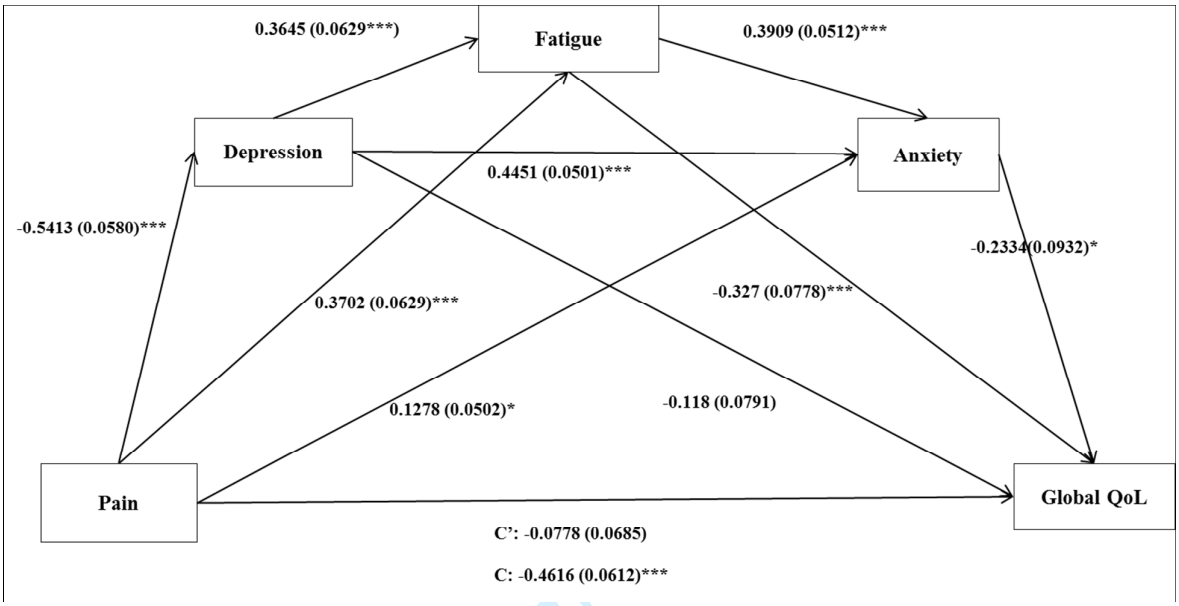
Figure 3. Serial mediation model 6 (SMM6) linking Pain and Quality of Life (n=212). Note: Standardized effects are presented outside the parentheses with bootstrapped standard errors in the parentheses. C' = Direct Effect of Pain to HRQoL; C=Total effect of Pain to HRQoL; Total Indirect effect = -0.384, 95% biased corrected C.I.:-0.51, -0.284; Ratio of Indirect to Total effect: 0.832, 95% C.I.:0.58-1.17; Model is controlled for Gender (i.e. type of cancer). *p < .05, ** p < .01, ***p < .001. Global fit indices: Chi-square=10.27(3), p=0.069, CFI=0.938, RMSEA=0.10(0.04, 0.18).



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Parallel and serial mediation analysis between Pain, Anxiety, Depression, Fatigue and Nausea, Vomiting and Retching within a randomised controlled trial in breast and prostate cancer patients

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Parallel and serial mediation analysis between Pain, Anxiety, Depression, Fatigue and Nausea, Vomiting and Retching within a randomised controlled trial in breast and prostate cancer patients.

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Abstract

Objective

Cancer treatment is a particularly stressful period for the patient. The reasons vary and include fear of treatment outcome as well as treatment induced side-effects. The patient frequently experiences simultaneously various side-effects resulting in a diminishing of the patient's health related quality of life-HRQoL. The study provides evidence on the co-occurrence and interrelations between pain, anxiety, depression and fatigue in breast and prostate cancer patients.

Design

This paper presents a secondary analysis of the data from a randomised control trial designed to test the effectiveness of Guided Imagery and Progressive Muscle Relaxation on pain, fatigue, anxiety and depression. Non-parametric bootstrapping analyses were used to test the meditational model of Anxiety, Fatigue and Depression as parallel mediators of the relationship between Pain and HRQoL. The ClinicalTrials.gov NCT01275872

Setting

The study was undertaken at the home setting

Participants

In total 208 patients were included in the study (assigned equally in two groups), referred at the out-patient clinics of the three participating cancer care centres.

Results

The three mediators fully mediate the relationship between Pain and HRQoL ($IE_{overall}$=-0.3839, 95% C.I.: LL=-0.5073, UL=-0.2825) indicating that patients with increased Pain are

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likely to have higher levels of Anxiety, Fatigue and Depression. Gender significantly moderated the mediational effect of Fatigue (IMM=-0.2867 SE=0.1526, LL=-0.6127, UL=-0.0226) but did not moderate mediational effect of Anxiety (IMM=-0.0709, SE=0.1414, LL=-0.3459, UL=+0.2089). The results show that the three mediators in a serial causal order fully mediate the relationship between Pain and HRQoL ($IE_{overall}$=-0.384, 95% C.I.: LL=-0.51, UL=-0.284) and the ratio of the overall indirect effect to the total effect, is 0.8315 (95% CI: LL=0.5683, UL=1.1718).

Conclusion

This work provides evidence that targeting fatigue, anxiety and depression may have a meaningful effect on pain as a related symptom and potentially have a positive impact on HRQoL of breast and prostate cancer patients.

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Strengths and Limitations of the Study

- Understanding the mediating effects of symptoms within a cluster will explain how these are manifested in clinical practice.
- The findings will have important clinical implications and could guide symptom cluster management strategies.
- The study provided evidence that as part of a management strategy, by targeting fatigue, anxiety and depression may have a meaningful effect on pain.
- Rigorous design and implementation allow for the generalizability of the findings in these group of patients.
- The unavailability of longitudinal data limits the support of a definite model, which would demonstrate if the correlations between symptoms found in this study are stable over time.

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Introduction

Cancer treatments and cancer itself are a source of many symptoms and side-effects [1-2] It is reported that on average cancer patients experience 11 to13 concurrent symptoms, whilst for patients with advanced disease the number can be even greater [3]. Often these symptoms are related to each other, called symptom clusters (CSs) or symptom constellations[3]. Dodd et al[4-6] defined symptom cluster as 3 concurrent and related symptoms that may or may not have a common etiology. However, the authors suggested that a cluster can be composed of just 2 or more symptoms that form a stable group[3]. Symptoms can be related through a common mechanism or etiology, by sharing common variance, or by producing different outcomes than individual symptoms.

The impact of these clusters can be accumulative and debilating for the patient and far more serious and persistent than single symptoms. Their concurrent presence make their clinical management complex and challenging. As a result, these clusters can affect the patient's overall Health Related Quality of Life-HRQoL [7] and significantly affect the patient's sense of wellbeing and his or her physical and social functions [8].

A number of studies have tried to record the most common clusters in various cancer types[4,9], however due to the lack of agreement about a robust, clinically relevant definition of SCs, their results should be interpreted with caution. Although the groups of symptoms that tended to cluster were identified, there is limited consistency in the way in which these SCs and their associated variables were identified[1].

Preceding studies, again by drawing on the weaknesses of the clinical definition of a SC, they provide limited information towards understanding the way (or ways) the symptoms are actually correlated to each other or to other variables (i.e. HRQoL). Most of the models

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available adopt a serial mediation approach to the study of these clusters, suggesting a rather linear correlation between the symptoms.

According to the definition by Dodd et al[4] for example, a cluster of pain, fatigue and insomnia is presented as a legitimate one. However the authors supported that pain leads to fatigue and in turn insomnia and this is a rather linear representation. Therefore the rationale for examining these symptom clusters within the mediational models is to explicate whether these symptoms can have an alternative way of interaction other than the one suggested in a linear way. What is further lacking in the current research is the role of other possible mediators such as cancer diagnoses which is also explored within this study.

These limitations are present with other SCs that have been identified so far in the literature leaving a gap to the best understanding of this phenomenon but most importantly to the way it can be best clinically managed. When interventions are directed to ameliorate a particular symptom within a cluster, other symptoms within the cluster may be relieved. However this evidence is not available to the best of our knowledge in the suggested mediational models available in the literature. As a result, current practice is driven based on *a priori* assumptions about the relationships among symptoms resulting in targeting the "dominant" symptom. In the previous example, pain would have been identified as a "dominant" symptom and therefore secondary attention is attributed to any other symptom that co-occurs.

These *a priori* assumptions are however not based on scientific evidence but rather have been established on clinical experience. However, a symptom cluster experienced by the patient creates a complex condition where pain is rarely reported as a single symptom, but as a distressing symptom is reported and addressed in a timely manner. However, the lack of knowledge in the ways symptoms might correlate to each other and with other variables, the question remains whether the dominant symptom in these situations is indeed pain. The

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question that also arises is whether there would be a clinical benefit if for example pain and fatigue are correlated and interventions were specifically designed to target both symptoms. The researchers so far had hypothesised that it is pain and this has become the common practice dominating the current clinical management of this specific SC. This study hypothesises that in the mediational models to be tested within this cluster of symptoms, fatigue, anxiety and depression will be identified as mediating factors in the pain HRQoL linkage. Furthermore, the study hypothesises that the mediation role of anxiety, depression and fatigue will differ between the breast cancer and prostate cancer diagnoses.

Aim

The aim of this study was to provide evidence on the co-occurrence of and interrelations between symptoms occurring as part of a cluster in two groups of patients diagnosed with breast and prostate cancer.

Methods

The data for the purpose of this paper came from a Randomised Control Trial (NCT01275872) designed to test the effectiveness of Guided Imagery (GI) and Progressive Muscle Relaxation (PMR) on a cluster of symptoms reported by patients diagnosed with breast or prostate cancer when receiving chemotherapy[10]. The patients in the study reported the following symptoms: fatigue, pain, nausea, vomiting and retching, anxiety and depression.

Measurements

The data were collected through the use of appropriate valid and reliable measures. The pain intensity was assess through a 10-point numeric rating scale (NRS) for pain where 0 indicated

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the absence of pain and 10 indicated the worst experienced level of pain. Within the cancer context, NRS used to assess the intensity of pain have a proven validity and reliability [11].

The Cancer Fatigue Scale (CFS)[12], was used to assess the participants' levels of fatigue. The CFS consists of three dimensions with 15 items that assess patients' responses on physical, affective, and cognitive aspects of their daily living. A 5-point Likert scale is used to assess each of the items where 1 denotes "not at all" to 5 which denotes "very much". The possible scores range from 0 to 28 for the physical, 0 to 16 for the affective, and 0 to 16 for the cognitive subscale. The CFS had good stability (average test–retest reliability $r = 0.69$, $P < 0.001$) and good internal consistency (Cronbach's alpha coefficient for all 15 items = 0.88)[13].

Nausea and vomiting was assess through the Revised Rhodes index of nausea, vomiting and retching (INVR)[14] which consists of eight 5-point self-reported items designed to assess subjective and objective factors of nausea, vomiting and retching. The validity and reliability of the INVR in cancer patients has been demonstrated in preceding studies [15].

The levels of anxiety were assessed with the Zung self-rating anxiety scale-SAS which contains 20 items that assess physiological and psychological symptoms commonly associated with anxiety, and each item is answered on a 4-point Likert-type scale ranging from "never" to "always" [16]. Raw scores sum to 20–44 that signify normal anxiety levels, 45–59 signifying mild to moderate anxiety levels, 60–74 signifying moderate to severe anxiety levels, and finally 75–80 indicating extreme anxiety levels. The scale's validity and reliability in cancer populations has been established in previous studies [17].

The Beck Depression Inventory-II has been utilised to assess patients' level of depression according to 21 items that correspond to a specific symptom common among people with depression [18]. Each item is evaluated on a 4-point scale ranging from zero to three. The

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number of items' responses is summed to indicate the severity of depression as follows: 1–10 is considered normal, 11–16 indicated mild mood disturbance, 17–20 indicates borderline clinical depression, 21–30 represents moderate depression, 31–40 represents severe depression, and over 40 indicates extreme depression. The Beck Depression Inventory has been extensively used in cancer populations where it demonstrated excellent validity and reliability [19].

As with the majority of studies that explore symptom and symptom management, Quality of Life is a frequently reported outcome that has been used to demonstrate the negative impact of symptoms but also to reflect on the effectiveness of symptom management strategies. HRQoL was included in the study due to the consistent evidence in the literature that the cluster of symptoms is associated to poor levels of quality of life in patients diagnosed with cancer[20, 21, 7]. Therefore, HRQoL has also being introduced in this study as a variable that can be correlated to the studied symptoms. The HRQoL of the patients was assessed with the EORTC QLQ-C30 module in addition to the module BR23 for breast cancer patients and the module PR25 for prostate cancer patients. The EORTC QLQ-C30 includes five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and a number of single items assessing additional symptoms (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease. The research items are assessed on a Likert scale ranging from 1 to 4 (1 = "not at all"; 2 "a little";3 "quite a bit"; 4 "very much"). Only the last two items assessing overall health and overall QOL are assessed on a scale ranging from 1 (very poor) to 7 (excellent) [22]. The EORTC QLQ-C30 module has a proven record of excellent validity and reliability across different cancer populations and languages [23].

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The BR23 is a breast-specific module that comprises of 23 questions to assess body image, sexual functioning, sexual enjoyment, future perspective, systemic therapy side effects, breast symptoms, arm symptoms and upset by hair loss. The questions of the module are assessed on a Likert scale ranging from 1 to 4 (1 = “not at all”; 2 =“a little”; 3 =“quite a bit”; 4 =“very much”). The validity and reliability of the BR23 module has been demonstrated in breast cancer populations [24].

The PR 25 prostate-specific module consists of 25 items across 6 scales: urinary symptoms, incontinence aid, bowel symptoms, hormonal treatment-related symptoms, sexual active, and sexual function. The module includes 5 conditional questions, conditioned on the need of incontinence aid, and the status of being sexually active. The questions of the module are assessed on a Likert scale ranging from 1 to 4 (1 = “not at all”; 2 =“a little”; 3 =“quite a bit”; 4 =“very much”). The validity and reliability of the PR25 module has been extensively demonstrated in prostate cancer populations [25].

Sample

As the rationale for this study was to test the correlations between symptoms identified as clusters, only the baseline (T0) measurements from both groups (intervention and control group) were included in the analysis. Based on predetermined criteria, 208 patients were included in the study. The sample included 104 female breast cancer patients (52 in control group + 52 in intervention group) and 104 prostate cancer patients (52 in control + 52 in intervention).

Statistical analysis

Non-parametric bootstrapping analyses[26] were deployed to test the meditational model of Anxiety, Fatigue and Depression as parallel mediators of the relationship between Pain and HRQoL. The nausea, vomiting and retching were excluded from the analyses as these were not

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found to correlate with the other symptoms. In these analyses, mediation is significant if the 95% Bias Corrected and accelerated confidence intervals (Lower Limit - LL), Upper Limit (UL) for the indirect effect do not include 0[8, 26]. Moreover, separated regression analyses were deployed to explore the statistical association of Cancer diagnosis and Age of the patient with the HRQoL.

Three mediation models are hypothesized and explored. The first model is a cancer diagnosis adjusted parallel mediation model of indirect effect of Pain to HRQoL through Anxiety, Fatigue and Depression. The second model is a moderated mediation model where the indirect effects of the mediating factors are explored on each cancer diagnosis (conditional indirect effects). The third model assumes a serial causal chain of the three mediators (serial mediation). Six different causal chains were explored in this model.

All involved variables in the analyses were standardized (z scores) before running the analyses, hence standardized coefficients are reported for the Total, Direct and Indirect effects.

Analysis was performed by utilising the PROCESS function v.2.16.1 in SPSS v.21. The model 4 (model as a parameter in the PROCESS function) was used for the parallel mediation model, model 15 (moderated mediation) for the second mediation model and model 6 for the serial mediation models[27].

Model fit is also reported using the following: a chi-square (df, a comparative fit index (CFI)>0.90 and a root mean square error approximation (RMSEA) of <0.10. The fit indices were derived using the package *lavaan* in R[28].

Ethics

The study was compliant to the Declaration of Helsinki and the protocol was approved by the Cyprus National BioEthics Committee (ID CNBC/EP/2010/06). All participants signed an

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informed consent prior to their inclusion in the study. A detail presentation of the study's methodology is presented elsewhere[29].

Patient and Public Involvement statement

As part of the study, a group of patients with relevant diagnoses were consulted in identifying the study's research question and relevant hypotheses. The patients were not directly involved in the design of the study nor in the recruitment and carrying out of the study. The authors intend to disseminate results to study participants through written summaries; academic outputs will be publicised through traditional media channels and social media.

Results

Sample characteristics

The sample consisted of 104 male (52 in the intervention group and 52 in the control group) and 104 female (52 in the intervention group and 52 in the control group) patients diagnosed with prostate and breast cancer. Eighty-six of the prostate cancer patients were diagnosed with stage T3a, Gleason score 8, and the remaining 18 with stage T3b, Gleason score 9. Patients with breast cancer were all diagnosed with clinical stage T3N1M0. Most of the participants belong to the 41-50 and the 51-60 age groups (38.9% and 26.4% respectively). Prostate cancer patients were treated either with a combination of androgen deprivation therapy (ADT) and adjuvant chemotherapy or with a combination of androgen deprivation therapy (ADT) and radiation (65.3% and 19.2% respectively).

The correlation analysis shows that HRQoL is negatively associated with Pain (r=-0.462), Fatigue (r=-0.601), Anxiety (r=-0.595) and Depression (r=-0.510) indicating that lower quality of life is associated with higher levels of the psychological aspects as well as Pain. Furthermore,

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Pain is positively correlated with all psychological aspects and negatively correlated with HRQoL (Table 1).

Covariates

Age was not found to be statistically associated with the level of HRQoL either on the Total Effects model (b=-1.13 p=0.27, Predictors of HRQoL: Pain, Sex, Age) or on the Direct Effect model (b=-0.9903 p=0.2866, Predictors to HRQoL: Anxiety, Fatigue, Depression, Pain, Gender, Age).

Gender was found to be statistically associated with the HRQoL in the Total Effects model (b=-7.2972 p=0.0143) indicating that female patients experienced lower quality of life compared to male patients. Therefore, gender which in this study also reflects the type of cancer, is included in the mediation models as a statistical control variable.

Parallel mediation model

Results based on 5000 bootstrapped samples indicated that, controlling for the gender, whilst the total effect of Pain on HRQoL was significant (β_{total}=-0.4616, SE=0.0612, p<0.001), the direct effect was not (β_{direct}=-.0778, SE=0.0685, p=0.2576) and indirect effects (IE) are present (Figure 1).

Overall, the three mediators fully mediate the relationship between Pain and HRQoL ($IE_{overall}$=-0.3839, 95% C.I.: LL=-0.5073, UL=-0.2825) indicating that patients with increased Pain are more likely to have higher levels of Anxiety, Fatigue and Depression. Patients through the experience of high levels of Anxiety, Fatigue and Depression, are more likely to report lower levels of Quality of Life.

Two out of the three mediators were found to significantly contribute to the overall indirect effect. Specifically, there is as statistically significant indirect effect of Pain to HRQoL though

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Anxiety ($IE_{anxiety}$=-0.1378, 95% C.I.: LL=-0.2615, UL=-0.0395), such that participants who indicated high levels of Pain were more likely to feel Anxiety, and through high levels of Anxiety, more likely to report lower levels of HRQoL. In addition, there is as statistically significant indirect effect of Pain to HRQoL though Fatigue ($IE_{fatigue}$=-0.1856, 95% C.I.: LL=-0.2716, UL=-0.1093), such that patients who indicated high levels of Pain were more likely to feel Fatigue, and through high levels of Fatigue, more likely to report reduced HRQoL. Depression does not mediate the relationship between Pain and HRQoL ($IE_{depression}$=-0.0605, 95% C.I.: LL=-0.1575, UL=+0.0289).

Specific indirect effect contrasts between the proposed mediators do not show statistically significant difference between the indirect effects of Anxiety and Fatigue (b=0.0478, 95% CI: LL=-0.260, UL=0.0822). The ratio of the overall indirect effect to the total effect, is 0.8315 (95% CI: LL=0.5683, UL=1.1718), while the ratio of the Anxiety and Fatigue indirect effects to the Total effect is 0.2985 (95% CI: LL=0.0758, UL=0.5711) and 0.4020 (LL=0.2230, UL=0.6317) respectively.

Moderated mediation model – Cancer diagnosis moderation

The current analysis tests whether the indirect effect of Pain to HRQoL through Anxiety or Fatigue is moderated by cancer diagnosis, i.e. whether the mediation effect observed earlier, is statistically significantly different in prostate cancer patients and breast cancer patients.

A moderated mediation model is explored where Anxiety and Fatigue act as parallel mediators and diagnosis as a moderator (Figure 2) to the mediation. The proposed model is under model 15 of the PROCESS documentation[27] where the moderation effect takes place at the B-Path (Mediator to Dependent) and at the C- path (direct path: Independent to Dependent). Model 15 (moderation effect not included to the A-path), was chosen over Model 59 (moderation effect on all paths) since separate regression analysis for the interaction of Diagnosis to the

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relationship of the Independent (Pain) to the Mediators (Anxiety and Fatigue) did not reach statistical significance. The slope of the line relating the indirect effect to the moderator is the "index of moderated mediation" (IMM)[28].The statistical significance of the IMM effect is assessed along with the conditional indirect effects across each cancer diagnosis.

Diagnosis significantly moderated the mediational effect of Fatigue (IMM=-0.2867 SE=0.1526, LL=-0.6127, UL=-0.0226) but did not moderate mediational effect of Anxiety (IMM=-0.0709, SE=0.1414, LL=-0.3459, UL=+0.2089). This means that there is a meaningful difference in the magnitude of the conditional indirect effects of each cancer diagnosis in the mediation effect of Pain to HRQoL through Anxiety. Specifically, we observe that for prostate cancer patients the conditional indirect effect is trivial and not statistically significant (β=0.0746, SE=0.1474, LL=-0.1893, UL=+0.3853) but for breast cancer patients the conditional indirect effect is stronger than prostate cancers' and statistically significant (β=-0.2121, SE=0.0434, LL=-0.307, UL=-0.1351) (Table 2). Fatigue is a significant mediator to the relationship between Pain and HRQoL in breast cancer patients rather than prostate cancer patients. There is no meaningful difference in the mediating effect of Anxiety for the relationship between Pain and HRQoL between prostate and breast cancer diagnoses.

Serial mediation model

Serial mediation hypothesizes a causal chain linking of the mediators (Anxiety, Fatigue, Depression), with a specified direction flow. For example, Pain, could increase Anxiety, which in turn increases Depression which could in turn increase Fatigue and thus decrease Quality of Life. (i.e., Pain->Anxiety->Depression-Fatigue->HRQoL).

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The results show that the three mediators in a serial causal order (any order that is) ***fully mediate*** the relationship between Pain and HRQoL ($IE_{overall}$=-0.384, 95% C.I.: LL=-0.51, UL=-0.284) and the ratio of the overall indirect effect to the total effect, is 0.8315 (95% CI: LL=0.5683, UL=1.1718). The total indirect effect and the ratio to the total effect, both are the same as in the parallel mediation model explored earlier.

Since three mediators were used, six different causal order models were produced (Table 3). All six models were compared in terms of the significant path created by each different causal order of the mediators. SMM 1, SMM 2 and SMM 4 yielded only three significant indirect paths out of the 7 possible paths, whereas SMM 3, SMM 5 and SMM6 yielded 4, 5 and 6 significant paths respectively.

SMM 3, SMM 5 and SMM 6 yielded a significant indirect path involving all 3 mediators in a causal chain. The path *Pain->Depression->Anxiety->Fatigue->HRQoL* in SMM 3 yielded the highest ratio of indirect to total effect; 0.126 (95% C.I.: 0.056-0.248) among the three models (Table 3).

The indirect paths involving *Fatigue* and *Depression* (one after the other and vice-versa) were statistically significant in 1 out of the 6 SMMs and specifically in SMM6.

The indirect paths involving *Anxiety* and *Depression* (one after the other and vice-versa) was statistically significant in 3 out of the 6 SMMs and specifically in SMM3, SMM5, and SMM6

The indirect paths involving *Fatigue* and *Anxiety* (one after the other and vice-versa) were statistically significant in all SMMs. This result means that increased Pain increases Fatigue (or Anxiety) which in turn increase Anxiety (or Fatigue) resulting in a decreased Quality of Life. The serial causal effect of these two mediators was found significant in any casual order of the mediators in place.

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Figure 3 depicts the effects of the direct paths linking pain to each mediator and among mediators resulting from the SMM 6 in which all the direct and indirect effects are statistically significant. The positive signs (+ve) of the effects are indicative of the increased Anxiety, Fatigue and Depression that increased Pain causes. Moreover, it shows that increased levels of each mediator is associated with a positive effect (i.e. increase) in the levels of the mediator with a direct connection. All indirect paths from Pain to HRQoL are negative, showing the reduction in HRQoL levels through the increase in the levels of the mediators. The SMM 6 results show that the worst the Pain was the more it would contribute to Depression, higher depression resulted to higher Fatigue, higher Fatigue led to higher levels of Anxiety which in turn contributed to lower HRQoL.

Discussion

The aim of this study was to explore the co-occurrence and interrelations between symptoms that were reported by two cancer patient groups and HRQoL. With previous findings showing that these symptoms can be present in different clusters in these groups of patients [30,31], we specifically aimed to demonstrate that pain, depression, fatigue, nausea, vomiting and retching and anxiety can form a common symptom cluster over the course of breast cancer and prostate cancer treatment. The findings showed that with the exception of nausea, vomiting and retching, the symptoms of pain, fatigue, anxiety and depression formed a common symptom cluster in both breast and prostate cancer patients. The findings also showed that HRQoL is negatively associated with pain, fatigue, anxiety and depression. This suggests that with these two groups of patients the symptoms consisting of the cluster need to be addressed collectively not only emphasizing on pain management but also focusing on depression, anxiety and fatigue. This provides a more comprehensive symptom management to the patient with also a positive effect on the HRQoL.

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Parallel, serial and moderate mediation analyses yielded interesting results in relation to symptom correlations. Parallel mediation analysis showed that the three mediators (fatigue, anxiety, and depression) fully mediate the relationship between Pain and HRQoL. However, whilst Anxiety and Fatigue were found to significantly contribute to the overall indirect effect, Depression did not mediate the relationship between Pain and HRQoL. The results demonstrated the mediating effect of these symptoms on pain and HRQoL, however at the same time the results supported the notion that "pain" needs to be targeted first. Although the data used for the analysis cannot support a definite model as these data were not longitudinal, however it does suggest that researchers and clinicians should consider these alternative correlations between symptoms and HRQoL. For example, cancer diagnosis significantly moderated the meditational effect of Fatigue but not Anxiety. Therefore, for prostate cancer patients conditional indirect effect is minimal but for breast cancer patients the effect is stronger and statistically significant. With the existence of many complex variable correlations being recorded in the literature in isolated symptom studies, these new findings suggest that conflicts in preceding studies may be resolved by the increased understanding of variable interaction in symptom clustering.

The exact underlying mechanisms by which symptoms correlate with each other are not to this date fully understood and this is an area that could contribute in the comprehensive management of symptom clusters through the development of effective multimodal interventions for breast and prostate cancer patients for use in the active treatment phase. A variety of non-pharmacological interventions have been proposed for treating pain, fatigue, depression and anxiety including exercise, psychosocial, cognitive behavioural, and nutritional[32-34]. However, most of these recommendations are proposed for use in single symptom management, perhaps with the exception of guided imagery and progressive muscle relaxation that its effectiveness was also tested in symptom cluster[29]. Further research is

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needed towards examining whether multimodal interventions can reduce pain and, in turn, reduce depression, fatigue and anxiety.

Clinical decision making in symptom management is traditionally driven by the type of the symptom rather than its impact on the patient or its correlations to other symptoms that might simultaneously be present. Preceding studies[35] consistently showed that emphasis is given on pain management rather than management of other symptoms such as fatigue or anxiety within a clinical situation where a symptom cluster manifests. The main problem with these patterns in symptom management is that despite the knowledge that symptoms co-exist; these are prioritised according to perceived importance. However, the correlation between the symptoms is purposively not taken into consideration including the likelihood that by treating for example Fatigue in breast cancer patients, the results of any pain management intervention might be fortified as well as the positive impact on HRQoL. On the same example, treating Fatigue in prostate cancer patients will most likely have no accumulating effect on the patient's responsiveness to pain management interventions. This example highlights that within the clinical setting such clinical decision making has also an impact on the cost-effectiveness of the symptom management interventions, as resources can be purposively allocated to other symptoms or variables that mediate pain and HRQoL to maximise clinical management.

The study has some limitations. The main limitation is the small sample size; however, several statistically significant paths emerged and within-symptom paths were replicated across both study samples (i.e cancer type groups). The unavailability of longitudinal data limits the support of a definite model, which would demonstrate if the correlations between symptoms found in this study are stable over time. However, the fact that the patients in the study were all in the active treatment phase strengthens the generalisability of the results to patients with prostate and breast cancer during this phase.

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The study demonstrated that pain, depression, fatigue, and anxiety tend to co-occur during the treatment phase, thus providing further evidence for this symptom cluster in two distinct samples of breast and prostate cancer patients. The study also showed the direct and indirect effects of this symptom cluster on the person's HRQoL. Parallel mediation analysis showed that the three mediators (fatigue, anxiety, and depression) fully mediate the relationship between Pain and HRQoL. Similarly, in a serial causal order, the three mediators fully mediate the relationship between Pain and HRQoL. The moderated mediation analysis showed that Diagnosis significantly moderated the mediational effect of Fatigue but did not moderate mediational effect of Anxiety. There are explicit clinical implications of the study's findings that include assessment, prevention, and intervention for anxiety, depression, fatigue and pain related to breast and prostate cancer treatment. This work provides preliminary evidence that targeting fatigue, anxiety and depression may have a meaningful effect on pain as a related symptom and potentially have a positive impact on HRQoL of patients with breast cancer and prostate cancer.

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Competing Interests

None declared

Data Statement

Data are available from the Cyprus University of Technology given that the Cyprus National BioEthics Committee will grant access to data for researchers who meet the criteria doe

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access to confidential data. There are no unpublished data from this study. Data requests can be sent to the corresponding author at andreas.charalambous@cut.ac.cy

Author Statement

The authors of this paper have directly participated in all the stages of its preparation. Authorship statement: AC conceived and designed the study, analyzed, interpreted the data and approved the final manuscript. MG prepared all the draft versions of the manuscript. MG, LP recruited the participants, interpreted the data and edited and approved the final version of the manuscript. AC, MG, EB collected the data. LP performed the statistical analysis and interpretation of the data. AC, MG, LP interpreted the data, edited and approved the final version of the manuscript. AC, LP were responsible for the financial support.

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Table 1: Pearson correlation coefficients between the variables

	Pain	Fatigue	Anxiety	Depression	HRQoL
Pain	1				
Fatigue	,567**	1			
Anxiety	,590**	,715**	1		
Depression	,541**	,565**	,735**	1	
HRQoL	-,462**	-,601**	-,595**	-,510**	1

** p<0.001

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Table 2: Conditional indirect effect(s) of PAIN on HRQoL at Gender and Index of Moderated Mediation

Mediators	Moderator (Gender)	β(SE)	95% Confidence Interval
Anxiety			
	Male	0.1324 (0.1314)	(-0.4076, 0.1138)
	Female	-0.2033 (0.0578) *	(-0.3315, -0.1026)
Fatigue			
	Male	0.0746 (0.1463)	(-0.2015, 0.3574)
	Female	-0.212 1(0.0436) *	(-0.3034, -0.1282)

Moderated Mediation Index

Mediator	β(SE)	95% Confidence Interval
Anxiety	-0.0709 (0.143)	(-0.3583, 0.2094)
Fatigue	-0.2867 (0.156) *	(-0.5996, -0.0057)

*p<0.05, Bias corrected bootstrapped Confidence Intervals, 5000 bootstrap samples. Statistically significant moderated mediation occurs only for Fatigue. Although there is a significant conditional indirect effect for Females through the mediator Anxiety, the difference between the conditional indirect effect for Males is not significantly different than that of the Females.

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Table 3: Standardised indirect effects and ratio of indirect to total effects for the paths on the serial mediation models.

	Indirect effects of Pain on HRQoL		Ratio of indirect to total effect	
	b (boot SE)	BC 95% CI [LB-UB]†	b (boot SE)	BC 95% CI [LB-UB] †
SMM1: PN -> AXT -> DEP -> FTG -> HRQoL				
PN -> AXT -> HRQoL	-0,138 (0,057)	(-0,268, -0,04)	0,299 (0,126)	(0,082, 0,581)
PN -> AXT -> DEP -> HRQoL	-0,042 (0,033)	(-0,109, 0,022)	0,091 (0,074)	(-0,049, 0,239)
PN -> AXT -> FTG -> HRQoL	-0,108 (0,032)	(-0,186, -0,057)	0,234 (0,077)	(0,114, 0,424)
PN -> AXT -> DEP -> FTG -> HRQoL	-0,004 (0,01)	(-0,028, 0,013)	0,009 (0,022)	(-0,029, 0,063)
PN -> DEP -> HRQoL	-0,018 (0,018)	(-0,069, 0,005)	0,04 (0,04)	(-0,012, 0,153)
PN -> DEP -> FTG -> HRQoL	-0,002 (0,005)	(-0,019, 0,005)	0,004 (0,011)	(-0,01, 0,041)
PN -> FTG -> HRQoL	-0,071 (0,024)	(-0,13, -0,033)	0,154 (0,056)	(0,07, 0,296)
SMM2: PN -> FTG -> AXT-DEP -> HRQoL				
PN -> FTG -> HRQoL	-0,186 (0,042)	(-0,272, -0,11)	0,299 (0,126)	(0,082, 0,581)
PN -> FTG -> AXT -> HRQoL	-0,074 (0,032)	(-0,146, -0,023)	0,244 (0,077)	(0,119, 0,427)
PN -> FTG -> DEP -> HRQoL	-0,002 (0,006)	(-0,022, 0,006)	0,088 (0,074)	(-0,047, 0,241)
PN -> FTG -> AXT -> DEP -> HRQoL	-0,022 (0,018)	(-0,063, 0,011)	0,003 (0,008)	(-0,007, 0,029)
PN -> AXT -> HRQoL	-0,064 (0,03)	(-0,141, -0,018)	0,158 (0,058)	(0,071, 0,304)
PN -> AXT -> DEP -> HRQoL	-0,019 (0,017)	(-0,062, 0,008)	0,002 (0,005)	(-0,004, 0,024)
PN -> DEP -> HRQoL	-0,018 (0,017)	(-0,067, 0,005)	0,038 (0,039)	(-0,012, 0,147)
SMM3: PN -> DEP>AXT -> FTG-- -> HRQoL				
PN -> DEP -> HRQoL	-0,061 (0,048)	(-0,156, 0,03)	0,131 (0,106)	(-0,072, 0,343)
PN -> DEP -> AXT -> HRQoL	-0,074 (0,031)	(-0,15, -0,021)	0,161 (0,07)	(0,044, 0,324)
PN -> DEP -> FTG -> HRQoL	-0,006 (0,015)	(-0,043, 0,018)	0,014 (0,032)	(-0,038, 0,094)
PN -> DEP -> AXT -> FTG -> HRQoL	-0,058 (0,019)	(-0,105, -0,028)	0,126 (0,047)	(0,057, 0,248)
PN -> AXT -> HRQoL	-0,064 (0,029)	(-0,138, -0,019)	0,138 (0,065)	(0,042, 0,306)
PN -> AXT -> FTG -> HRQoL	-0,05 (0,017)	(-0,094, -0,025)	0,108 (0,038)	(0,053, 0,212)
PN -> FTG -> HRQoL	-0,071 (0,024)	(-0,13 , -0,033)	0,154 (0,056)	(0,07 , 0,296)
SMM4: PN -> AXT -> FTG -> DEP> -> HRQoL				
PN -> AXT -> HRQoL	-0,138 (0,056)	(-0,262 , -0,04)	0,299 (0,125)	(0,076 , 0,578)
PN -> AXT -> FTG -> HRQoL	-0,113 (0,031)	(-0,187 , -0,061)	0,244 (0,076)	(0,122 , 0,426)
PN -> AXT -> DEP -> HRQoL	-0,041 (0,034)	(-0,115 , 0,02)	0,088 (0,075)	(-0,045 , 0,259)
PN -> AXT -> FTG -> DEP -> HRQoL	-0,001 (0,004)	(-0,013 , 0,003)	0,003 (0,008)	(-0,007 , 0,028)
PN -> FTG -> HRQoL	-0,073 (0,025)	(-0,131 , -0,031)	0,158 (0,058)	(0,065 , 0,299)
PN -> FTG -> DEP -> HRQoL	-0,001 (0,003)	(-0,011 , 0,002)	0,002 (0,006)	(-0,004 , 0,022)
PN -> DEP -> HRQoL	-0,018 (0,017)	(-0,067 , 0,005)	0,038 (0,039)	(-0,01 , 0,152)
SMM5: PN -> FTG -> DEP>AXT -> HRQoL				
PN -> FTG -> HRQoL	-0,186 (0,042)	(-0,272 , -0,11)	0,402 (0,103)	(0,223 , 0,632)
PN -> FTG -> DEP -> HRQoL	-0,024 (0,019)	(-0,064 , 0,011)	0,052 (0,042)	(-0,023 , 0,146)
PN -> FTG -> AXT -> HRQoL	-0,052 (0,023)	(-0,106 , -0,016)	0,112 (0,051)	(0,031 , 0,23)
PN -> FTG -> DEP -> AXT -> HRQoL	-0,022 (0,011)	(-0,05 , -0,007)	0,049 (0,024)	(0,015 , 0,11)
PN -> DEP -> HRQoL	-0,036 (0,031)	(-0,106 , 0,016)	0,079 (0,069)	(-0,034 , 0,238)
PN -> DEP -> AXT -> HRQoL	-0,034 (0,015)	(-0,07 , -0,01)	0,073 (0,034)	(0,021 , 0,156)
PN -> AXT -> HRQoL	-0,03 (0,019)	(-0,082 , -0,004)	0,065 (0,042)	(0,008 , 0,181)
SMM6: PN -> DEP>FTG -> AXT -> HRQoL				

PN -> DEP -> HRQoL	-0,061 (0,048)	(-0,158 , 0,029)	0,131 (0,107)	(-0,065 , 0,355)
PN -> DEP -> FTG -> HRQoL	-0,065 (0,023)	(-0,12 , -0,03)	0,14 (0,054)	(0,062 , 0,283)
PN -> DEP -> AXT -> HRQoL	-0,056 (0,023)	(-0,111 , -0,017)	0,122 (0,053)	(0,033 , 0,245)
PN -> DEP -> FTG -> AXT -> HRQoL	-0,018 (0,009)	(-0,043 , -0,006)	0,039 (0,021)	(0,011 , 0,096)
PN -> FTG -> HRQoL	-0,121 (0,031)	(-0,192 , -0,07)	0,262 (0,073)	(0,146 , 0,44)
PN -> FTG -> AXT -> HRQoL	-0,034 (0,016)	(-0,073 , -0,011)	0,073 (0,035)	(0,021 , 0,16)
PN -> AXT -> HRQoL	-0,03 (0,019)	(-0,082 , -0,004)	0,065 (0,042)	(0,008 , 0,181)

Notes: Table shows standardized indirect effects with bootstrapped standard errors; Paths in bold indicate statistically significant indirect effects; PN=Pain, DEP=Depression, AXT=Anxiety, FTG=Fatigue, HRQoL = Quality of Life; $^{\int}$ Bias Corrected 95% confidence intervals; SMM=Serial Mediation Model

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Figure Legends

Figure 1. Parallel Mediation Model (n=208). Indirect effects of Pain on Global HRQoL through Anxiety, Fatigue and Depression. Note: Model is controlled for the cancer diagnosis. Standardized effects are presented. The effects on the direct path from Pain to Global HRQoL depict the Direct effect and the (Total effect). *p < .05, ** p < .01, ***p < .001

Figure 2. Moderated Mediation Model (n=208). Conditional Indirect effects on Cancer Diagnosis (Breast Cancer coded as 1 and Prostate Cancer as 0) of Pain on Global HRQoL through Depression. Note: Standardized effects are presented. The effects on the direct path from Pain to Global HRQoL depict the Conditional Direct Effects for each cancer diagnosis as well as the unconditional direct effect C' path (Total effect C-path). The effects of the moderator Diagnosis to the paths represent the interaction slopes. Effects on the B-paths from the mediators to HRQoL represent the simple slopes. *p < .05, ** p < .01, ***p < .001

Figure 3. Serial mediation model 6 (SMM6) linking Pain and Quality of Life (n=212). Note: Standardized effects are presented outside the parentheses with bootstrapped standard errors in the parentheses. C' = Direct Effect of Pain to HRQoL; C=Total effect of Pain to HRQoL; Total Indirect effect = -0.384, 95% biased corrected C.I.:-0.51, -0.284; Ratio of Indirect to Total effect: 0.832, 95% C.I.:0.58-1.17; Model is controlled for Cancer Diagnosis. *p < .05, ** p < .01, ***p < .001. Global fit indices: Chi-square=10.27(3), p=0.069, CFI=0.938, RMSEA=0.10(0.04, 0.18).

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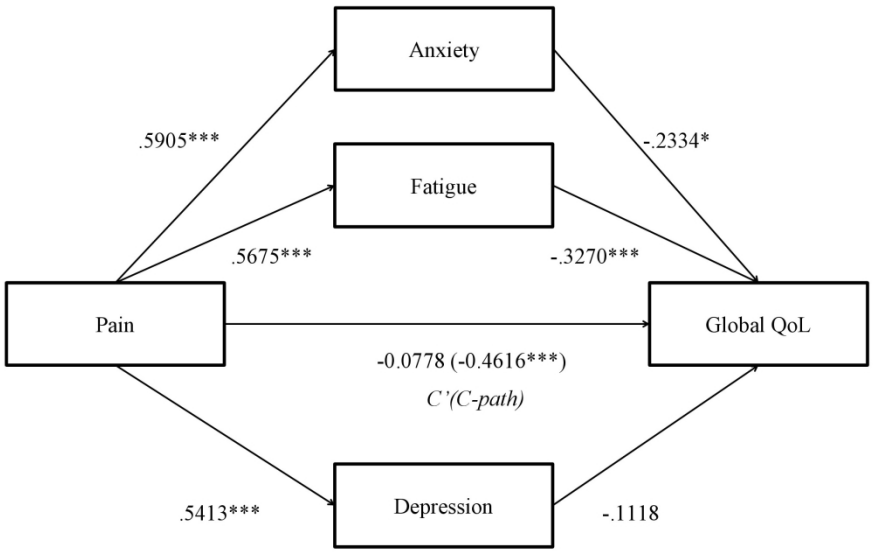

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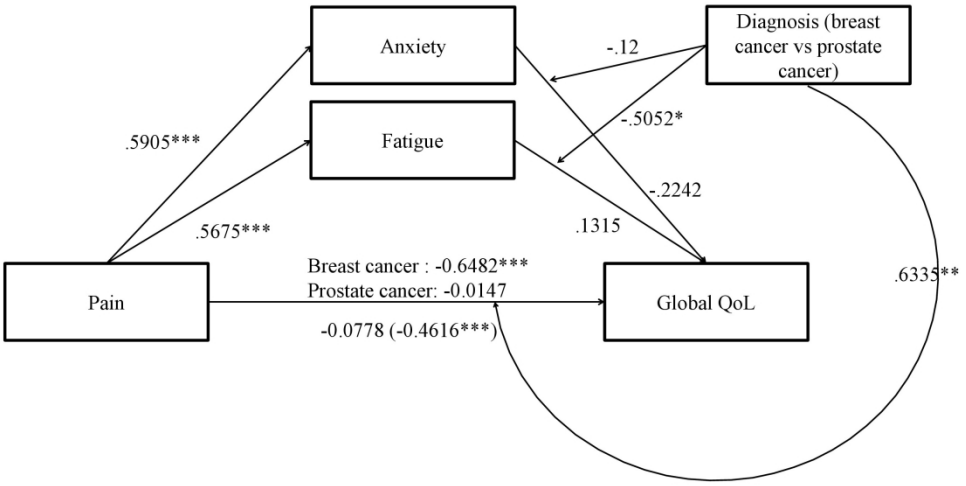

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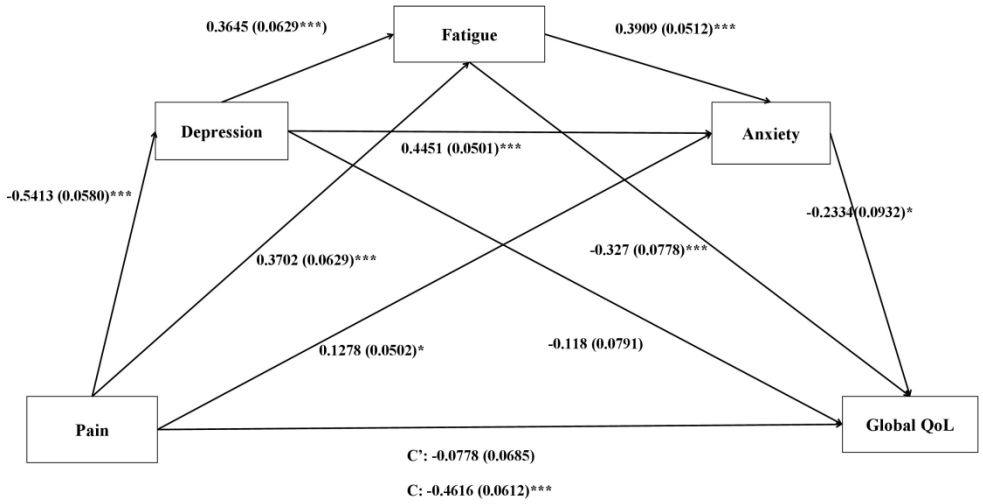

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243x129mm (300 x 300 DPI)