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Heterogeneity of posttraumatic stress, depression, and fear of cancer recurrence in breast cancer survivors: a latent class analysis

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Abstract

Purpose Breast cancer survivors may demonstrate elevated psychological distress, which can also hinder adherence to survivorship care plans. Our goal was to study heterogeneity of behavioral health and functioning in breast cancer survivors, and identify both risk and protective factors to improve targets for wellness interventions.

Methods Breast cancer survivors ($n = 187$) consented to complete self-reported psychological measures and to access their medical records. Latent class analysis (LCA) was used to classify heterogeneous subpopulations based on levels of depression, post-traumatic stress, fear of cancer recurrence, cancer-related pain, and fatigue. Multinomial logistic regression and auxiliary analysis in a 3-step modeling conditional approach was used to identify characteristics of the group based on demographics, treatment history and characteristics, and current medication prescriptions.

Results Three subpopulations of breast cancer survivors were identified from the LCA: a modal *Resilient* group (48.2%, $n = 90$), a *Moderate Symptoms* group (34%, $n = 65$), and an *Elevated Symptoms* group ($n = 17\%$, $n = 32$) with clinically-relevant impairment. Results from the logistic regression indicated that individuals in the *Elevated Symptoms* group were less likely to have a family history of breast cancer; they were more likely to be closer to time of diagnosis and younger, have received chemotherapy and psychotropic prescriptions, and have higher BMI. Survivors in the *Elevated Symptoms* group were also less likely to be prescribed estrogen inhibitors than the *Moderate Symptoms* group.

Conclusions This study identified subgroups of breast cancer survivors based on behavioral, psychological, and treatment-related characteristics, with implications for targeted monitoring and survivorship care plans.

Implications for Cancer Survivors Results showed the majority of cancer survivors were resilient, with minimal psychological distress. Results also suggest the importance of paying special attention to younger patients getting chemotherapy, especially those without a family history of breast cancer.

Keywords Cancer · Depression · PTSD · Stress · Fear of recurrence · Survivorship

Introduction

The incidence of cancer is rising, with breast cancer being one of the most common cancers: over 279,100 new cases were estimated in the USA in 2020 alone [1]. Treatment advances have led to an all-stage survival rate for female breast cancer at 90%, making the study of health and wellness in breast cancer survivorship an important area of study impacting a large population of survivors. After completing acute treatment, breast cancer survivors often have individual emotional and psychiatric needs in the survivorship period; maintaining psychological wellbeing in the face of evolving follow-up treatments, along with uncertainties about cancer recurrence, presents a formidable challenge [1].

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Despite generally resilient outcomes, longitudinal and prospective studies show that a significant subset of patients experience worsening or enduring distress after their cancer diagnosis [2–4]. High levels of emotional distress can have serious consequences by impairing self-management and access to available resources, including use of and adherence to supportive care services [5, 6]. A recent meta-analysis highlighted that depression and anxiety are associated with greater cancer recurrence, cancer-specific mortality, and all-cause mortality, with depression predicting a 30% increase in overall mortality risk [7]. Increased mortality risk for breast cancer patients with depression and anxiety was corroborated by a study of over 120,000 patients [8]. Moreover, breast cancer survivors may suffer from post-traumatic stress disorder (PTSD; [9]) and, more commonly, from fear of cancer recurrence (FCR) either in the same organ or another part of the body [10]. PTSD and FCR are associated with worse adherence [11] and reporting unmet clinical needs [12].

Taken together, the current literature suggests that depression, anxiety, and PTSD symptoms are among the most common psychiatric co-morbidities in breast cancer survivors with prevalence rates of approximately 30%, 20%, and 10%, respectively [9, 13]. How these different symptoms interact and their combined role in impacting breast cancer survivorship remains poorly understood. One underlying issue is that psychological reactions to cancer, as well as to other potentially traumatic events, are highly heterogeneous [14]. The presence of marked differences in individual reactions renders the examination of average effects in cancer survivors inefficacious if treated as one, single, homogenous group [15]. The resulting spuriousness hinders the identification of risk and protective factors to improve targeted treatment and ultimately outcomes.

An empirical solution is to tease apart broad psychological symptom and disorder heterogeneity across individuals by identifying subtypes through the use of computational methods. Person-centered techniques such as mixture modeling and latent class analysis (LCA; [16]) identify patterns in the data, leading to the characterization of subgroups (or classes) based on their differences and similarities across all examined characteristics jointly (e.g., psychiatric symptoms and medical features of interest). This is in contrast with variable-centered approaches examining a set of one or more predictors, which are based on the assumption that all individuals come from a single population that can be described accurately by pooled parameters (i.e., average scores) [17]. Patients grouped in one class by LCA are similar to each other and different from those in other groups (e.g., resilient vs chronic high symptoms patients) across all examined characteristics, serving as computational phenotypes for targeted treatment and prevention [20]. Thanks to its ability to identify heterogeneous patient groups, LCA can be applied to improve our understanding of the heterogeneity of psychopathological distress in breast cancer survivors similar to its prior successful application in the context of distress associated with medical conditions [18] and trauma [19].

Studies have begun to utilize LCA, or similar techniques, such as growth mixture modeling, to explore distinct groupings of breast cancer survivors likely to experience varying levels of distress or impaired physical functioning. For example, psychological adjustment to cancer was examined in 1294 adults over the course of six years, suggesting resilience as the modal response [2]. A more recent study of 968 female breast cancer survivors identified two longitudinal trajectories of symptom burden (low: 19%; high: 81%) based on symptoms of fatigue, pain, insomnia, breast, and arm symptoms [21]. Longitudinal trajectories of anxiety based on the Hospital Anxiety and Depression Scale (HADS) in 725 breast cancer survivors demonstrate two at risk groups: high stable symptoms of anxiety (6%) and elevated symptoms that decrease somewhat over time (16%; [22]). Studies including survivors of many types of cancer find similar patterns of a small subgroup with elevated clinical symptoms (e.g., [23]). However, while offering important contributions to the literature, these studies focused only on a handful of domains. Few studies have utilized LCA to examine classes of distress across several psychiatric symptom domains (including fear of cancer recurrence), quality of life, and physical symptoms (e.g., fatigue, pain) combined.

The current study examined psychiatric symptoms, functioning, and cancer treatment characteristics in an outpatient clinical sample of breast cancer survivors. We used LCA to better understand the heterogeneity of presentations in breast cancer survivors, based on comprehensive behavioral, psychological, and cancer treatment-related characteristics. Our goal was to identify subgroups with elevated psychological distress, medical difficulties, and low quality of life, and then to examine their associated characteristics as potential risk and protective factors. We hypothesized that breast cancer survivors could be divided into heterogeneous subgroups characterized across a range of different levels of depression, PTSD, stress, and anxiety sensitivity. Moreover, we hypothesized these groups would be further characterized by differences in quality of life, fatigue, and fear of cancer recurrence. Lastly, we examined the association between heterogeneous psychiatric distress and functioning levels with cancer treatment characteristics, demographics, and current medication regimen.

Method

Participants and procedures

Participants were adult breast cancer survivors (ages 18 and above) with a breast cancer diagnosis at least 6 months

prior to recruitment. Potential participants were identified through medical record review and subsequent consultation with their treating oncologists or nurse practitioners. Individuals receiving current chemotherapy or palliative care services as well as those with Stage IV breast cancer were excluded from the study. Potential participants meeting initial eligibility criteria were contacted via multiple methods, including email, mail, and messaging through the electronic medical record system. Participants who indicated interest were consented prior to study procedures. Procedures were approved by the Institutional Review Board at NYU Grossman School of Medicine.

Measures

Differences and similarities among breast cancer survivors were examined based on relevant demographics, behavioral health measures, medication regimens, medical comorbidities, cancer, and cancer treatment characteristics [1, 24]. To collect this information, individual medical records were accessed with consent to collect information on participants' medical health. In addition, participants completed a set of self-report questionnaires in a single session via REDCap or through a mailed paper version (depending on preference).

Demographics

Demographics of interest included age, gender, education, race/ethnicity, current employment status, marital status, and household income.

Depression, anxiety, and stress

Depressive symptoms were measured using the 8-item version of the Patient Health Questionnaire (PHQ-8; [25]), a self-report measure that is effective for detecting depression in cancer patients [26]. A score ≥10 has been established as a useful threshold for detecting current depression [25]. The 16-item Anxiety Sensitivity Index (ASI; [27]) assessed fear of anxiety-related sensations; clinical elevation is defined as ASI≥20 [28]. The Perceived Stress Scale (PSS; [29]) assessed the degree to which current situations in survivors' daily lives were appraised as stressful. Ranges of 0–13, 14–26, and 27–40 have been recommended to categorize low, moderate, and high perceived stress (e.g., [30–32]).

Fear of cancer recurrence and post-traumatic stress

The 9-item Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF; [33]) was used to evaluate cancer-specific worries, concerns, and uncertainty about health status and illness returning and has an established cut-off score of ≥22 to indicate clinically significant levels of FCR. Post-traumatic stress symptoms were measured using the 20-item PTSD Checklist for DSM-5 (PCL-5; [34]), which was anchored to cancer and its treatment as the index trauma. A preliminary suggested cut score for threshold symptoms on the PCL-5 was 33; however, recent validation studies suggest cut scores as low as 28 may capture a symptomatic population [35].

Survivorship quality of life, pain, and fatigue

Quality of life was measured using the Functional Assessment of Cancer Therapy-General (FACT-G; [36]), a 28-item self-report measure assessing physical, social/family, emotional, and functional well-being in cancer patients. Physical pain was assessed using the Short-form McGill Pain Questionnaire 2 (MPQ; [37]), a 24-item self-report questionnaire of different qualities of pain and related symptoms felt during the past week. The 14-item Fatigue Symptom Inventory (FSI; [38]) was used to assess the severity, frequency, and daily pattern of fatigue as well as its perceived interference with quality of life in cancer patients.

Medical health information

Collected medical information included current medication regimen, cancer stage, cancer diagnosis data, cancer treatment modalities (e.g., chemotherapy, hormone treatment), and family history of breast cancer. In addition, current body mass index (BMI), the BMI at time of cancer diagnosis (to calculate pre/post BMI loss), and presence of common medical comorbidities among survivors (i.e., hypertension, arthritis, diabetes, thyroid problems; [24]) were also collected.

Data analysis

Latent class analysis (LCA) was performed via MPLUS version 8 [39] to identify heterogeneous subgroups of cancer survivors. LCA is a population-based statistical method that empirically determines heterogeneity by identifying sub-groups of individuals in a sample (i.e., latent classes) who share similar multidimensional characteristics among them. Latent class indicators variables were selected from behavioral health measures (i.e., depression, anxiety, stress, fear of cancer recurrence, and PTSD) and cancer treatment related wellbeing (i.e., quality of life, pain, and fatigue), to determine groupings based on psychological characteristics. Successively, differences among subgroups in terms of demographics, medication regimen, and cancer treatment were further investigated.

Prior to the conditional analyses, missing data for covariates and auxiliary variables were imputed through chained equations via the package MICE in R [40], using five multiple imputations. Psychological variables from the unconditional LCA were hidden during the imputation process to

avoid information leakage. Following imputation, covariates with categorical data were converted into binary variables based on modal frequencies, while continuous variables were centered and scaled. All scales were normalized using min-max transformations prior to modeling.

First, nested unconditional LCA models with increasing numbers of classes were compared to determine the best-fitting model. Examined model fit indices included Bayesian information criterion (BIC), sample-size adjusted Bayesian information criterion (SSBIC), relative entropy, Lo–Mendell–Rubin–adjusted likelihood ratio test (LMR LRT), and bootstrapped likelihood ratio test (BLRT). The best fitting solution was determined based on model fit indices (i.e., lowest information criteria, highest entropy, statistically significant LRTs), as well as based on parsimony and explanatory properties [41].

After determining the solution for the number of classes with the best fit, we analyzed treatment, medication regimen, and demographic variables nested as covariates in a conditional LCA. In addition, cancer stages (i.e., I, II, or III), the number of months passed and BMI loss since breast cancer diagnosis were included as auxiliary variables using a 3-step modeling approach [42]. In the LCA conditional model, multinomial logistic analyses determined the association of covariate and auxiliary variables with class membership of heterogeneous subgroups of cancer survivors.

Results

Sample characteristics

Among the cancer center outpatients, 949 individuals with a history of breast cancer were contacted of whom 191 consented to study participation. Participation rate in the study was 20%, and chi square analysis indicated no difference with non-participants in terms of referring doctor ($X^2(6, n = 949) = 3.03$, $p = .80$) or cancer stage ($X^2(2, n = 949) = 1.82$, $p = .40$). The final sample consisted of 187 outpatients with a history of breast cancer who consented and completed the full survey. Table 1 reports their full characteristics. Participants were predominantly women, white, well-educated, and with a household income higher than the state median. The most common breast cancer stage was IA ($n = 100$), followed by IIA ($n = 47$). Average BMI was in the overweight range ($M = 26.11$, SD = 5.69), with high cholesterol and high blood pressure as primary reported comorbidities. The vast majority of individuals (94%, $n = 174$) were receiving hormone therapy for breast cancer at the time of the study, consisting primarily of either tamoxifen (i.e., a selective estrogen receptor modulator; 44%, $n = 81$) or letrozole (i.e., a non-steroidal aromatase inhibitor, which decreases the synthesis of estrogen; 36%, $n = 67$). The majority of patients had been administered chemotherapy cycles in the past (59% $n = 109$). Moreover, about half of the sample was also still receiving some form of cancer-related treatment (51%, $n = 95$), including cytotoxic (e.g., paclitaxel, $n = 68$), and immune suppressor (e.g., cyclophosphamide, $n = 66$) medications. More than half were taking psychiatric medications (59%, $n = 110$), with benzodiazepines as the most common prescription (33%, $n = 62$).

Heterogeneous subgroups

LCA nested unconditional model fit indices with 1 to 4 classes are reported in Table 2. Model fit indices suggested that the four class solution had the best information criteria and significant BLRT test. However, the LMR LRT for the 4-class model was not significant, suggesting that the one-less class solution could have a more appropriate fit. Results of the LMR LRT, in conjunction with theoretical considerations about parsimony [41], pointed to the three class model which also had the best fit among the remaining solutions (i.e., lower BIC and SSBIC, higher relative entropy, significant LMR LRT, and BLRT tests). Therefore, the three class model was chosen as the optimal solution.

The best fitting LCA of breast cancer survivors in our sample is displayed in Figure 1. The model identified three heterogeneous subpopulations that were distinct based on their levels of psychiatric symptoms, cancer treatment-related pain, and quality of life. Probability of distinct class membership for each individual outpatient was very high, with values ranging from .92 to .97. The largest subgroup of breast cancer survivors (*Resilient*; 48.2%, $n = 90$) was characterized by an asymptomatic presentation and good functioning. Specifically, they reported low levels of PTSD (PCL-5: $M = 3.85$, SD = 3.9), depression (PHQ-8: $M = 1.3$, SD = 1.48), and stress (PSS: $M = 9.56$, SD =5.24) symptoms and low anxiety sensitivity (ASI: $M = 12.64$, SD = 9.93). In terms of cancer-related measures, they reported low levels of fear of cancer recurrence (FCRI: $M = 14.76$, SD = 5.99), low pain (MPQ: $M = 7.54$, SD = 2.92), low fatigue (FSI: $M = 15.22$, SD = 11.49), as well as high quality of life (FACT-G: $M = 91$, SD = 8.05). The second largest class (*Moderate Symptoms*; 34.8%, $n = 65$), endorsed subclinical levels of PTSD (PCL-5: $M = 15.07$, SD = 8.69), depression (PHQ-8: $M = 5.07$, SD = 2.27), and stress (PSS: $M = 9.56$, SD = 5.24) symptoms, with mean anxiety sensitivity just above the recommended clinical threshold (ASI: $M = 21.38$, SD = 11.57). The *Moderate Symptoms* group showed higher levels of fatigue (FSI: $M = 15.48$, SD = 4.86), pain (MPQ: $M = 42.68$, SD = 19.52), and FCRI ($M = 21.23$, SD = 6.21), as well as lower quality of life (FACT-G: $M = 76.64$, SD = 8.28). Lastly, the final group (*Elevated Symptoms*, 17%, $n = 32$) consisted of individuals who endorsed clinical levels of PTSD (PCL-5: $M = 33.13$, SD = 11.88) and depression

Table 1 Sample demographic and clinical characteristics

Variable	M (SD), Median (IQR) or % (*n*) *n* = 187
Gender: *Female*	99% (186)
Age	57.7 (12.5)
Race:	
White	87% (161)
Black/African American	7% (13)
Asian	4% (8)
Other	2% (4)
Ethnicity: *Hispanic/Latino*	4% (7)
Body Mass Index (BMI)	26.11 (5.69)
Household Income	
≥ $100,000	*65% (93)*
$75,000–$99,999	*14% (20)*
$50,000–$74,999	*14% (20)*
$0–$49,999	*8% (11)*
Full-time employment	54% (100)
Education (*n* = 186)	
College Graduate or more	85% (159)
Partial College	12% (22)
High School Diploma or Less	3% (5)
Marital status	
Married or living with partner	51% (95)
Single	30% (57)
Divorced, separated, or widowed	19% (35)
Time since diagnosis (months)	35 (21–63)
Cancer stage	
IA	54% (100)
IB	0.5% (1)
IIA	25% (47)
IIB	10.5% (19)
IIIA	7% (13)
IIIC	3% (6)
Cancer treatment types (*n* = 184)	
Current hormone therapy	66% (121)
Received chemotherapy	60% (110)
Family history of breast/ovarian cancer	41% (76)
Medical comorbidities	
High cholesterol	21% (39)
High blood pressure	20% (38)
Arthritis	16% (30)
Thyroid diseases	8% (15)
Musculoskeletal disorders	5.9% (11)
Lung diseases	5.4% (10)
Heart disease	3.2% (6)
Other	3.2% (6)
Medication regimen (n = 186)	
Hormone therapy (1 or more)	94% (174)
Tamoxifen	44% (81)
Letrozole	36% (67)

Table 1 (continued)

Variable	M (SD), Median (IQR) or % (*n*) *n* = 187
Cancer therapy (1 or more)	51% (95)
Paclitaxel	37% (68)
Cyclophosphamide	35% (66)
Psychiatric medication (1 or more)	60% (110)
Diazepam	33% (62)
Lorazepam	28% (52)
Behavioral assessments	
FCRI: Fear of Cancer Recurrence Inventory (*n* = 170)	18.6 (7.3)
PCL-5: PTSD Checklist-5 (*n* = 173)	8 (3–19)
PHQ-8: Patient Health Questionnaire Depression (*n* = 176)	3 (1–7)
ASI: Anxiety Sensitivity Index (*n* = 173)	17 (8–27)
PSS: Perceived Stress Scale (*n* = 176)	14 (7.1)
FACT-G: Functional Assessment of Cancer Therapy (*n* = 159)	82 (71–93)
MPQ: McGill Pain Questionnaire 2 (*n* = 174)	8 (6–12)
FSI: Fatigue Symptom Inventory (*n* = 170)	29.5 (11–55)

Table 2 Fit indices for 1 to 4 class of latent class analysis

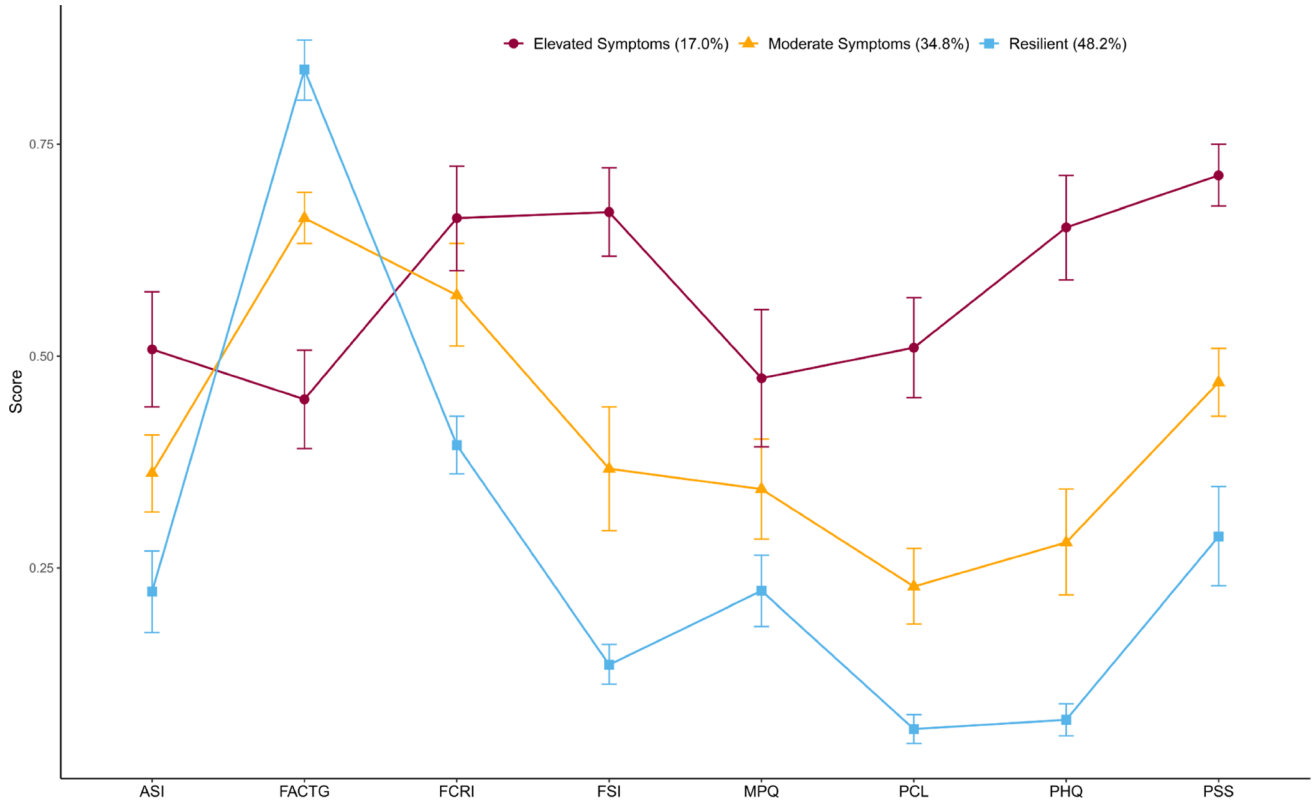
Statistics	1 Class	2 Classes	3 Classes	4 Classes
Bayesian information criteria	−225.83	−688.71	**−832.90**	841.91
Sample-size adjusted BIC	−276.5	−767.88	**−940.57**	−978.09
Entropy	-	.92	**.89**	.92
Lo-Mendell-Rubin adjusted LRT	-	498.76	**186.77**	54.43
P-value	-	*<.0001*	***<.05***	*.27*
Bootsrapped LRT *P*-value	-	*<.0001*	***<.0001***	*<.0001*

(PHQ-8: $M = 11.83$, SD = 3.17) symptoms, higher anxiety sensitivity (ASI: $M = 29.61$, SD = 11.46), and moderate levels of perceived stress (PSS: $M = 23.55$, SD = 4.01). They also reported elevated FCRI ($M = 24.14$, SD = 6.22), treatment-related pain (MPQ: $M = 11.61$, SD = 3.99), and fatigue (FSI: $M = 76.81$, SD = 16.81), as well as overall lower quality of life (FACT-G: $M = 59.85$, SD = 13.86). Of note, the 95% confidence intervals suggested that the *Moderate* and *Elevated Symptoms* group share similar FCRI and cancer-related pain, despite their differences in levels of endorsed psychiatric symptoms.

Multinomial logistic regression

Conditional LCA analysis was performed to assess the role of patients' characteristics in their association to psychiatric symptoms and cancer-related functioning. Treatment characteristics, medication regimen, and demographic variables were nested as covariates in the model, while cancer stage, time passed, and BMI loss since cancer diagnosis were included as 3-step auxiliary variables. The conditional model converged successfully with an increased entropy score of .91, and there were no substantial changes in the shape and proportions of the trajectories from the unconditional solution.

Results from the multinomial logistic regression analyses (Table 3) indicated that among the three groups, the *Elevated Symptoms* individuals were significantly younger, with higher BMI as well as less likely to have a family history of breast cancer. When compared to the *Resilient* group, both the *Elevated* and *Moderate Symptoms* groups were more likely to have a history of chemotherapy treatment and to be currently taking psychiatric medications. In addition, the *Moderate Symptoms* individuals were more likely to have a letrozole prescription than the *Elevated* group. Moreover, the *Elevated Symptoms* group patients were diagnosed with breast cancer more recently than the *Resilient* individuals. No meaningful differences emerged between the heterogeneous subgroups in terms of cancer stage or other examined variables. Table 3 reports the logistic regression full estimates and their confidence intervals.



ASI = Anxiety Sensitivity Index; FACTG = Functional Assessment of Cancer Therapy-General; FCRI = Fear of Cancer Recurrence Inventory; FSI = Fatigue Symptom Inventory; MPQ = McGill Pain Questionnaire; PCL = PTSD Checklist for DSM 5; PHQ = Patient Health Questionnaire; PSS = Perceived Stress Scale.

Fig. 1 Latent Class Analysis of psychopathology symptoms in breast cancer survivors ($n = 187$)

Discussion

The current investigation is one of few known studies to tease apart heterogeneity of symptoms and characteristics associated with breast cancer survivorship based on medical records, several validated self-report measures across multiple psychiatric symptom domains (including fear of cancer recurrence) as well as functioning, and computational methodology. Our results suggest that the majority of breast cancer survivors showed a psychologically resilient pattern characterized by low distress, high quality of life, and low functional impairment (*Resilient*, 48.2%, $n = 90$). Moreover, 34% of individuals ($n = 65$) demonstrated *Moderate Symptoms*, although within the subclinical range for psychiatric symptoms but with more functional and cancer-related impairments. Lastly, a notable group of 17% (*Elevated Symptoms*, $n = 32$) endorsed elevated symptoms and impairment in the clinical range across all measures. These results show that a significant subset of breast cancer survivors experience ongoing depression, anxiety, and stress reactions into the survivorship period [2–4], and align with previous research including a recent study examining latent class memberships of breast cancer survivors across time following cancer treatment [43]. In this study of 198 female breast cancer patients, approximately 30% demonstrated high distress, marked by negative coping and high depression, immediately post cancer treatment with an increase in high distress group membership at 6 months post-treatment (35.42%) and a decrease and stabilization by 12- to 24-month post-treatment at 21.21% and 22.77% membership, respectively [43]. As our participants were on average 35-month post-diagnosis, our high distress group likely best aligns with those in the 24-month post-treatment group, which may represent individuals with stable distress post-diagnosis and treatment. Our results also align well with a study of 232 cancer survivors (25.7% breast cancer) which identified three latent classes, including a class with more compromised physical functioning (40%) but moderate distress, similar to our *Moderate Symptoms* class, as well as high clinical importance (14%) and low clinical importance (46%) classes, which appear similar to our *Elevated Symptoms* and *Resilient* classes [23]. Other studies utilizing LCA in cancer populations have also found similar patterns of

Table 3 Multinomial logistic regression for predictors of class membership ($N = 187$)

	Reference: Resilient						Ref: Moderate symptoms		
	Elevated symptoms			Moderate symptoms			Elevated symptoms		
Variable	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age	**0.94**	**[0.89–0.99]**	**.02**	0.98	[0.93–1.03]	.474	**0.95**	**[0.91–1.00]**	**.046**
BMI, Current	**1.18**	**[1.06–1.3]**	**.002**	0.99	[0.91–1.08]	.888	**1.18**	**[1.05–1.33]**	**.004**
Education (College+)	2.04	[0.32–13.16]	.452	1.19	[0.27–5.23]	.813	1.71	[0.33–8.86]	.522
Race (Caucasian)	0.26	[0.04–1.82]	.176	2.10	[0.52–8.49]	.299	**0.13**	**[0.02–0.83]**	**.031**
Household income (>$70k)	0.52	[0.13–2.09]	.357	0.45	[0.14–1.5]	.195	1.14	[0.32–4.12]	.836
Family history of cancer	**0.10**	**[0.02–0.37]**	**.001**	0.94	[0.38–2.32]	.886	**0.10**	**[0.03–0.39]**	**.001**
Medications:									
Tamoxifen	0.27	[0.07–1.08]	.064	0.59	[0.23–1.48]	.26	0.46	[0.1–2.05]	.308
Letrozole	0.23	[0.05–1.13]	.07	1.24	[0.48–3.23]	.652	**0.19**	**[0.03–0.99]**	**.048**
Cancer med.	1.14	[0.35–3.76]	.828	1.86	[0.72–4.81]	.198	0.61	[0.16–2.3]	.469
Psychotropic med.	**9.02**	**[1.69–47.98]**	**.01**	**5.79**	**[1.99–16.88]**	**.001**	1.56	[0.32–7.6]	.583
Treatment:									
Cancer stage	1.04	[.48–2.23]	.925	1.36	[0.75–2.46]	.314	.76	[0.35–1.65]	.496
Received chemotherapy	**3.29**	**[1.16–9.29]**	**.025**	**2.51**	**[1.05–6.03]**	**.039**	1.31	[0.43–3.99]	.639
Months since diagnosis	**.00**	**[0.00–0.15]**	**.009**	.48	[0.03–8.01]	.608	**.00**	**[0.00–0.30]**	**.018**
BMI, loss (pre/post treatment)	1.80	[0.7–4.63]	.220	1.43	[0.66–3.08]	.361	1.26	[0.47–3.38]	.644

Ref reference class, *OR* odds ratio, *95% CI* 95% confidence interval, *Med.* medication, *BMI* body mass index

groupings, typically with a small subgroup of high distress participants (e.g., 6–23%; [21–23, 43]).

Results from our LCA also indicated that the subgroups showed similar levels of distress for all psychopathology measures, regardless of the different constructs underlying each measure (e.g., PHQ-8 for depression, PCL-5 for PTSD). This finding is consistent with current practices in oncology, where behavioral health is often screened using shorter measures such as the single-item Distress Thermometer [44]. In addition, *Moderate* and *Elevated* symptomatic groups had comparably high levels of both pain and fear of cancer recurrence. This difference compared to the non-symptomatic *Resilient* groups suggests that these measures could serve as first level screening, and that amongst those with high pain and FCR, additional psychiatric symptom assessment may be helpful.

Further analyses showed characteristics of breast cancer survivors that were associated with the heterogeneous subgroups and their different levels of psychological distress. Of note, survivors who were treated with chemotherapy were more likely to be in the *Elevated* and *Moderate* groups, aligning with previous findings suggesting chemotherapy was associated with high stable anxiety following cancer treatment over time [22]. Moreover, individuals in these high distress subgroups were younger and closer in time to their breast cancer diagnosis, when compared to individuals in the *Resilient* group. These findings are in line with other literature which found increased risk of anxiety and depression and lower perceived quality of life in younger breast cancer survivors compared to older survivors; this was attributed to various factors, including a stronger sense of identity, better coping skills regarding medical illness, and less disruption of intimate relationships leading to less isolation and loneliness in the older cohort [45]. In addition, individuals with no family history of breast or ovarian cancer were more likely to be in the *Elevated Symptoms* group. This finding aligns with previous research, suggesting that women with a family history of breast cancer reported lower levels of distress [46] or distress in a similar, low range [47] when attending mammography breast cancer screening compared to women without a family history of breast cancer. Similarly, family history of cancer was not predictive of psychological distress for women referred for a breast cancer examination [48]. On the other hand, cancer-related distress has been shown to be high in newly diagnosed breast cancer patients [49] as well as in sisters of newly diagnosed patients [50] without a family history of breast cancer. Lower levels of distress in those with a family history of breast cancer may be demonstrative of having a model for coping with the disease. This may serve to increase predictability and reduce uncertainty, which may be associated with increased fear of cancer recurrence, anxiety, and distress [51, 52].

In terms of current medication regimen, breast cancer survivors taking psychiatric medications were predictably more likely to be in the *Elevated* and *Moderate Symptoms* distress groups. More interestingly, survivors taking

letrozole (a non-steroidal aromatase inhibitor which lowers estrogen production) were more likely to be in the *Moderate Symptoms* than in the *Elevated Symptoms* group. There is a growing body of literature on the role of estrogen in fear and stress-based pathology [53], suggesting that the hormone modulates fear extinction [54]. Inhibition of fear extinction may be a particularly relevant mechanism for our breast cancer survivor sample, as the two symptomatic subgroups both experienced elevated fear of cancer recurrence. It is therefore possible that differences between participants with subclinical (*Moderate*) and clinical (*Elevated*) symptom subtypes could also correspond to differences in activation of fear neurocircuitry (including the amygdala and ventromedial prefrontal cortex) due to lower estrogen levels, although more research is needed to directly examine this possibility. Further, while our analyses accounted for age, results could have also been influenced by the fact that the *Elevated Symptoms* group was younger and thus less likely to be post-menopausal, which is when letrozole is more commonly prescribed. Nonetheless, previous studies have shown that patients on estrogen blockers demonstrated increased rates of depression, given estrogen's downstream effects of enhancing serotonin and norepinephrine activity [55]. Overall, these results suggest that further study on the modulating role of estrogen and changes in cycles to anxiety, stress, and PTSD symptoms would be an important avenue of research, particular in the context of breast cancer survivorship plans where estrogen modulation is a common mechanism of therapeutic action.

Breast cancer survivors with higher BMI were also more likely to be in the *Elevated Symptoms* group, which had a mean BMI in the overweight range ($M = 27.70$, SD = 5.57), and was more elevated than the *Resilient* group ($M = 24.70$, SD = 5.64). Obesity in breast cancer patients has been previously associated with higher levels of distress [56], including in previous studies using LCA [23], depression [57], worse mental and physical health [58], and body dissatisfaction [59, 60]. As many as 50–96% of women report weight gain after breast cancer treatment [61]. Notably, results also align with previous findings suggesting that weight gain has been associated with receiving chemotherapy, as well as chemotherapy followed by endocrine treatment [61, 62], which also had a differential effect in elevated and moderately distressed individuals in our sample. Our findings suggest that early identification of breast cancer survivors reporting high distress who also have BMI in the overweight/obese range may be important given targeted lifestyle interventions that are efficacious for promoting weight loss and increasing quality of life. Indeed, several reviews and meta-analyses report efficacy of lifestyle interventions, such as exercise [63, 64], yoga [65], or the Mediterranean diet [66] for not only improving quality of life but also reducing risk of cancer recurrence in breast cancer survivors. Therefore, these interventions may be important to integrate into survivorship care plans, especially for those at higher risk of distress and medical comorbidities.

Though this study has strengths including use of computational methods to identify heterogeneous subgroups of distress in breast cancer survivors, there are some limitations. First, the sample was largely homogenous with respect to race, ethnicity, and education, which may limit generalizability of findings; future studies in more diverse samples are warranted. Additionally, our response rate was low (20%) and sample size was relatively small compared to some other existing studies in cancer populations using LCA methods (e.g., [21, 67]), but in a similar range to others (e.g., [23, 43]). Second, the study was cross-sectional; therefore, prospective changes and changes over time in symptoms levels could not be examined. Longitudinal studies may be able to identify individuals at risk for stable profiles of high distress across several psychiatric symptom domains and allow for earlier targeted intervention for these individuals. Indeed, existing longitudinal studies have identified risk factors, such as financial difficulties, having chemotherapy, not having children, not living with a partner and poorer physical and social support, as predictive of highly stable anxiety or high symptom burden following treatment [21, 22]. However, few studies have examined trajectories beginning at diagnosis or including multiple distress and functioning markers (e.g., fear of cancer recurrence), similar to those we examined. Finally, while participants completed several self-report measures and information was collected from the medical record, other medical markers of interest were not able to be obtained including information on type of surgery and/or radiation if received by the patients. While we assessed for difference in chemotherapy, it is possible that this additional medical information or additional medical comorbidities could have further informed results and associations with the identified classes.

Despite these limitations, our results contribute to the growing literature using computational methods to examine distress patterns and have implications for clinical assessment and survivorship care plans. Early identification and continual monitoring of those with risk factors identified in our study (e.g., younger age, overweight/obese BMI, treatment with chemotherapy, no family history of breast/ovarian cancer) that make them more likely to fall in the high distress group may be useful to helping identify who may benefit from early intervention. Once identified, several evidence-based options to improve distress markers can be considered based on domain of pronounced distress. For example, cognitive behavioral therapy (CBT; [68, 69]) and mindfulness-based interventions [70] have been shown to be helpful in improving psychological distress, quality of life, fatigue, and insomnia in breast cancer patients. For those with pronounced fear of cancer recurrence, interventions including

mindfulness, managing uncertainty, and improving communication between patients and providers have been shown to be effective [71]. Lifestyle interventions, such as exercise and yoga, also have demonstrated effects on both mental and physical health in breast cancer patients [63–65]. Of note, breast cancer survivors in our sample reported high levels of interest in participating in these wellness options [72]. For those without a family history of breast cancer, additional counseling may be required to facilitate informed decisions about treatment options as well as to promote psychological adjustment to the diagnosis [49]. These efforts would help reduce long-term impairment by offering interventions and resources in a more targeted approach, with the ultimate goal of improving quality of life in breast cancer survivors.

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Availability of data and material The dataset analyzed during the current study is not publicly available due to containing protected health information, but are available from the corresponding author on reasonable request.

Code availability Available on request.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Matteo Malgaroli, Kristin L. Szuhany, Gabriella Riley, Carly D. Miron, and Jae Hyung Park. The first draft of the manuscript was written by Matteo Malgaroli, and all authors reviewed and/or commented on previous versions of the manuscript. All authors made significant contribution to the work, and approved the final manuscript.

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Declarations

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Ethics approval The questionnaires and methodology for this study was approved by the IRB at NYU Langone Health.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable

Conflict of interest In the past 36 months, Naomi M. Simon reports the following: (1) research grants from the Department of Defense, NIH, PCORI, American Foundation for Suicide Prevention, and Vanda Pharmaceuticals Inc.; (2) speaking/CME/consulting from Bionomics Limited, Praxis Therapeutics, Genomind, BehavR LLC, Engrail Therapeutics Inc., Cerevel, Aptinyx, and Wiley (Deputy Editor Depression and Anxiety); (3) Royalty from Wolters Kluwer (UpToDate) and APA Publishing (Textbook of Anxiety, Trauma and OCD Related Disorders 2020); and (4) equity (spouse) from G1 Therapeutics and Zentalis. Dr. Chachoua reports sitting on the board of Tilray. Matteo Malgaroli, Kristin L. Szuhany, Gabriella Riley, Carly D. Miron, Jae Hyung Park, Jane Rosenthal, and Marleen Meyers have no relevant conflicts of interest to report.

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