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Fluctuations in depression and anxiety predict dysregulated leptin among obese breast cancer survivors

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Abstract

Purpose Leptin influences inflammation and tumor growth and leptin signaling is often dysregulated among obese breast cancer survivors. This leads to a lack of satiety and, ultimately, risk for further weight gain. Breast cancer survivors also experience high rates of depression and anxiety, which are linked to leptin production. This study examined how a woman's anxiety and depressive symptoms, in combination with their obesity status, were associated with leptin.

Methods Breast cancer survivors ($n = 200$, stages 0–IIIa) completed a baseline visit before treatment and two follow-up visits, 6 and 18 months after treatment ended. Women completed anxiety and depression measures, and blood samples provided leptin data at each visit. This study related fluctuations in a survivor's own depression and anxiety (i.e., within-person effects), as well as average effects of depression and anxiety (i.e., between-person effects) to changes in leptin depending on BMI.

Results Obese survivors' leptin was significantly higher at visits when they had higher anxiety and depression symptoms than their own average level of symptoms. In contrast, within-person fluctuations in depression and anxiety were not related to leptin levels among non-obese survivors. No significant between-person effects of depression or anxiety on leptin emerged.

Conclusions Leptin is a critical risk factor for recurrence and further health consequences. Our findings highlight how psychological health influences leptin production among breast cancer survivors.

Implications for Cancer Survivors These results highlight a biological pathway that may facilitate further weight gain and health risks among distressed, obese breast cancer survivors.

Keywords Breast cancer survivors · Leptin · Anxiety · Depression · Obesity

Introduction

Breast cancer survivors experience serious psychological and physical health risks during survivorship [1]. Obesity amplifies these risks, heightening risk for hypertension, diabetes, coronary artery disease, and kidney disease [2]. Notably, obesity also increases the risk for breast cancer recurrence and obese breast cancer survivors are 30% more likely to die prematurely compared to their non-obese counterparts [3, 4]. These risks highlight the importance of targeting obesity in both cancer survivorship research and intervention and understanding the biological mechanisms by which obesity confers risk so that these processes can be disrupted.

Leptin, an important biological mechanism underlying obesity, regulates energy intake and suppresses food consumption in conjunction with other peptide hormones [5]. Leptin crosses the blood–brain barrier in response to fat consumption, signaling to the hypothalamus that satiety has been achieved [6, 7]. For non-obese people, high leptin levels are adaptive because high leptin helps regulate hunger and

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weight. However, people can become leptin-resistant, a phenomenon that frequently co-occurs with obesity in which cells become less responsive to leptin. In these situations, satiety signals do not reach the brain, ultimately resulting in a continued desire to eat [8–11]. In short, higher leptin levels may only be adaptive among non-obese individuals. Thus, it is critical to know a person's obesity status when examining leptin trajectories over time.

Fatigue, a common problem among breast cancer survivors, decreases the likelihood of engaging in physical activity, thereby fueling weight gain [12]. Weight gain among breast cancer survivors is common, contributing to heightened risk for obesity. Obesity can increase risk for cardiovascular morbidity among breast cancer survivors [13]. Leptin levels also impact health outcomes in breast cancer survivorship. High leptin levels increase cell proliferation and transformation in breast cancer, thus promoting both tumor development and growth [14–18]. Research also suggests that leptin increases breast cancer risk [19]. Thus, although dysregulated leptin production presents risks for both physically healthy women and breast cancer survivors, dysregulated leptin among survivors poses an additional threat to their physical wellbeing and quality of life by increasing risk for morbidity and mortality.

Along with weight gain, breast cancer survivors also commonly experience psychological distress throughout survivorship [20–23]. Psychological distress, including depressive and anxiety symptoms, can influence leptin production. Animal models highlight low leptin as a significant correlate of high anxiety [24]. Among humans, evidence has linked low leptin to higher anxiety and depressive symptoms independent of body mass index (BMI) [25]. Among pre-menopausal, physically healthy women, higher depressive, and anxiety symptoms were associated with lower leptin while controlling for BMI [26]. Women diagnosed with panic disorder also had lower levels of resting leptin compared to psychologically healthy controls [27]. One limitation of this prior work is that BMI has typically served as a covariate, thus not fully accounting for the role that obesity plays in leptin dysregulation, as described above. One study testing interactions between BMI and depressive symptoms among healthy adults found that higher depressive symptoms were associated with low and high fasting leptin among normal weight and overweight adults, respectively [28].

Anxiety and depression can impair survivors' physical functioning and quality of life. Furthermore, these psychological experiences are highly individualized, and what one woman considers a normal level of depression or anxiety may be very high or low for another woman. The current study used a novel approach to examine how anxiety and depression are associated with fasting leptin in breast cancer survivors across three visits. We assessed how both between-person differences in depression and anxiety levels and within-person changes in depression and anxiety over time, related to fluctuations in leptin across visits. The between-person component examines the relationship between anxiety/depression and leptin for one woman relative to another. In contrast, the within-person component provides a unique opportunity to understand changes in a survivor's own depression and anxiety change before and after treatment in addition to how these changes relate to leptin across survivorship. Given that BMI is an important driver of leptin production, we also tested whether BMI moderated the between- and within-person effects of depression and anxiety on leptin. We hypothesized that the links between depression and anxiety and leptin would be stronger in obese survivors than non-obese survivors.

Methods

Participants and procedure

Participants were women with a breast cancer diagnosis (n = 200, stages 0–IIIa) recruited from cancer clinics for a longitudinal parent study on fatigue and immune dysregulation. Sample characteristics are presented in Table 1. Women were

Table 1 Baseline characteristics of breast cancer survivors (N = 200)

	Mean (SD)	Number (%)
Age	55.97 (11.53)	
BMI	28.75 (7.24)	
Underweight (BMI < 18.5)	–	2 (1.0%)
Normal Weight (BMI 18.5–24.9)	–	74 (37.0%)
Overweight (BMI 25.0–29.9)	–	54 (27.0%)
Obese (BMI > 30.0)	–	70 (35.0%)
Physical comorbidities	.78 (1.31)	
Race		
White	–	155 (77.5%)
Black	–	32 (16.0%)
Asian American	–	8 (4.0%)
Other	–	5 (2.5%)
Cancer stage		
0	–	37 (18.5%)
I	–	89 (44.5%)
II	–	54 (27.0%)
IIIa	–	18 (9.0%)
Cancer treatment		
Surgery only	–	60 (30.0%)
Radiation and surgery	–	53 (26.5%)
Chemotherapy and surgery	–	33 (16.5%)
Radiation, chemotherapy, and surgery	–	52 (26.0%)
No longer menstruating	–	125 (62.5%)

SD, standard deviation; *BMI*, body mass index

recruited within 1–3 months after their diagnosis to complete (a) a baseline visit before cancer treatment and (b) two follow-up visits, 6 and 18 months after treatment ended. Visit 2 occurred, on average, a little over 1 year (M = 13.45 months, SD = 5.43) following the first visit while visit 3 occurred approximately 1 year following visit 2 (M = 12.10 months, SD = 3.33). Women completed self-report questionnaires and provided a blood sample at each visit. Exclusion criteria included a diagnosis of stage IV breast cancer, a history of cancer except basal or squamous cell skin carcinomas and significant visual, auditory, or cognitive impairments. The Ohio State University Institutional Review Board approved the project and all participants provided written informed consent.

Predictors and moderators

Anxiety The 21-item Beck Anxiety Inventory (BAI) asked women to rate how frequently they experienced anxiety symptoms over the last month [29]. Scores on the BAI range from 0 to 63 with higher scores indicating greater anxiety symptoms. Cronbach's α for the BAI ranged from .79 to .85 across the three visits.

Depression The Center for Epidemiologic Studies Depression Scale (CES-D), commonly used in cancer patients, provided data on women's depressive symptoms [30]. The CES-D is a 20-item scale that asks participants to indicate the frequency at which they experienced depressive symptoms over the past week. Scores on the CES-D range from 0 to 60 with higher scores indicating greater depressive symptoms. Cronbach's α for the CES-D ranged from .89 to .91 across the three visits.

Body mass index Height and weight data from each visit were measured by a nurse and used to calculate BMI, which served as the moderator in all analyses. Consistent with prior research, BMI category was dichotomized for all moderation analyses (obese ≥ 30/not obese < 30) [3, 26, 31, 32].

Covariates

Potential confounds were included based on their theoretical and empirical relationships to anxiety, depression, and leptin. All models adjusted for treatment type, cancer stage, physical comorbidities, sleep, age, and post-menopausal status. The widely used Charlson comorbidity index, originally developed with breast cancer patients, provided data on physical comorbidities [33]. The measure assigns weight to 19 medical conditions (range, 1 to 37), with greater scores equal to greater comorbidity burden. The Insomnia Severity Index (ISI) provided data on sleep [34]. Scores on the ISI range from 0 to 28 with higher scores representing greater sleep difficulties.

Leptin collection

Fasting blood samples were collected between 7:00 and 10:00 AM. All blood samples for a woman were analyzed within the same assay run. Determinations for leptin were made using RIA kit instructions (Milipore Corporation, St. Charles, MO 63304). For leptin, the intra-assay coefficient of variation (CV) was 4.2% and inter-assay CV was 4.5%. Leptin sensitivity was 0.5 ng/ml. Leptin data was log transformed to better approximate normality of residuals.

Analytic plan

The sample size for this study was determined by a power analysis conducted for the parent study. SPSS Version 26 was used to conduct all analyses. Preliminary analyses examined correlations between and among the main study variables. Growth models examined trajectories of change in the key variables across visits using time as the predictor of depression, anxiety, BMI, and leptin.

Mixed linear models tested the primary hypothesis that depression or anxiety interact with BMI to predict leptin. This modeling approach accounted for the non-independence in participants' data (i.e., the correlation between an individual's scores on the same variable over time) and maximized the use of existing data by including all participants in the analyses, regardless of missing data points [35]; the mixed models used restricted maximum likelihood estimation, and a subject-specific random intercept captured the within-subject correlation. Depression, anxiety, and leptin were assessed at each visit, allowing for within-person and between-person analyses. Variables at the within-person level were person-centered so that participants' scores at each visit reflected how much higher or lower their depression and anxiety deviated from their own average across the study [36]. At the between-person level, depression and anxiety were grand-mean centered to represent the average associations between psychological distress and leptin across persons throughout the study. The within- and between-person effects of depression and anxiety were separated out by including the person-centered variable at level 1 and the between-person variable at level 2. Consistent with previous research, BMI was dichotomized (obese = BMI ≥ 30, non-obese = BMI < 30) and entered as an interacting variable in all models [3, 26, 31, 32]. Significant interacting effects were probed separately for obese and non-obese women. Models that included the interaction of BMI and between-person depression or anxiety did not converge and thus these interactions were removed from the final models.

Each model adjusted for physical comorbidities, age, sleep, post-menopausal status (yes; no), and visit (1; 2; 3) as time-varying (level 1) covariates, as well as treatment type (surgery only; radiation and surgery; chemotherapy and surgery; and

radiation, chemotherapy, and surgery) and cancer stage (0; I; II; IIIa) as time-invariant (level 2) covariates. All covariates were included in the final models. Continuous covariates were grand-mean centered to improve interpretability of the intercepts.

Results

Descriptive statistics

Table 1 provides descriptive statistics and frequencies of all control variables. Table 2 presents the means and standard deviations of the CES-D, BAI, and leptin at each visit. Across all survivors, growth models revealed that leptin did not change significantly across visits ($b = -.06$, SE = .07, $p = .35$). Depression ($b = 4.85$, SE = .72, $p < .001$) and anxiety ($b = 2.76$, SE = .59, $p < .001$) both decreased across visits. BMI increased significantly across visits ($b = .35$, SE = .22, $p < .01$). Table 3 provides bivariate correlations among depression, anxiety, leptin, BMI, and each covariate at visit 1.

Main effects of anxiety and depression predicting leptin across visits

Anxiety Between-person fluctuations in anxiety did not significantly predict leptin ($b = -10.94$, SE = 321.34, $p = .97$). During visits in which a woman's anxiety was higher than her average (i.e., within-person effects), she had higher leptin relative to visits when her anxiety was lower than her average ($b = 1317.14$, SE = 354.41, $p < .001$).

Depression Between-person fluctuations in depression did not significantly predict leptin ($b = 618.71$, SE = 274.24, $p = .06$). During visits in which a woman's depressive symptoms were higher than her average (i.e., within-person effects), she had higher leptin relative to visits when her depressive symptoms were lower than her average ($b = 1023.52$, SE = 310.61, $p < .01$).

Table 2 Study variable means and standard deviations ($N = 200$)

	Visit 1	Visit 2	Visit 3
Anxiety	11.91 (9.5)	9.68 (8.8)	9.09 (8.0)
Depression	11.36 (7.6)	7.20 (7.3)	7.04 (7.0)
Leptin	40.52 (42.17)	38.58 (36.06)	52.92 (69.98)
BMI	29.00 (7.30)	28.48 (7.07)	28.73 (7.14)

BMI, body mass index. Anxiety was measured using the Beck Anxiety Inventory. Depression was measured using the Center for Epidemiological Studies Depression Scale. Leptin means and standard deviations are measured in ng/ml and represent values prior to natural log transformation

Covariates In models with only the covariates included to predict leptin, post-menopausal survivors had significantly higher leptin compared to pre-menopausal women ($b = -.20$, SE = .09, $p = .02$). Physical comorbidities, cancer stage, treatment, and age were not related to leptin (all $ps > .25$).

Moderating effect of BMI on links between depression/anxiety and leptin

Anxiety BMI significantly interacted with anxiety at the within-person level to predict leptin ($b = 1235.38$, SE = 449.22, $p < .01$). As shown in Fig. 1, obese survivors' leptin was higher at visits where they were more anxious than usual compared to visits where they were less anxious than usual ($b = 1317.14$, SE = 354.41, $p < .001$). In contrast, leptin levels did not differ based upon within-person anxiety for non-obese survivors ($b = 81.76$, SE = 305.85, $p = .79$).

Depression The interaction between obesity and within-person depressive symptoms predicting leptin is presented in Fig. 2. Fluctuations in depressive symptoms at the within-person level interacted with BMI to predict leptin ($b = 940.88$, SE = 382.28, $p = .02$). Specifically, obese survivors had higher leptin levels at visits where their depressive symptoms were higher than usual compared to visits when their depressive symptoms were lower than usual ($b = 1023.52$, SE = 310.61, $p < .01$). The association between depression and leptin was not significant for non-obese survivors ($b = 82.65$, SE = 239.30, $p = .73$).

Discussion

Consistent with our hypotheses, this study demonstrated that at times when breast cancer survivors experienced higher than their usual levels of anxiety and depressive symptoms, they had higher leptin relative to when they were experiencing lower than usual levels (a within-person effect). This effect was moderated by BMI, such that within-person fluctuations in anxiety and depressive symptoms predicted leptin among obese, but non-obese, survivors. In contrast to these within-person effects, how a woman's depressive or anxiety symptoms compared to other survivors (between-person effects) was not associated with leptin levels. Accordingly, these results demonstrate how individual-level psychological functioning is related to leptin. These findings illustrate the utility of a within-person approach to examine how changes in a survivor's own symptoms impact leptin, and ultimately health, across time.

Among obese survivors, at visits where women had higher anxiety and depression compared to their own average, they also had higher fasting leptin. This is important because elevated leptin among obese survivors poses significant threats to their health and mortality, including increased risk for

Table 3 Baseline correlations among study variables

	1	2	3	4	5	6	7	8	9
1. Depression	-								
2. Anxiety	.76**	-							
3. BMI	.14*	.18*	-						
4. Leptin	.11	.09	.66**	-					
5. Age	− .30**	− .25**	.02	.18*	-				
6. Comorbidities	.01	.15*	.04	.05	.19*	-			
7. Menopause	− .09	− .07	.12	.19**	.68**	.13	-		
8. Cancer Tx	.12	.16*	.08	.07	− .15*	.02	− .12	-	
9. Stage	.02	.04	.20**	.26**	− .02	.00	.01	.45**	-

*$p < .05$, **$p < .001$; *BMI*, body mass index; *Cancer Tx*, cancer treatment type; *Stage*, cancer stage. Depression was measured using the Center for Epidemiological Studies- Depression scale. Anxiety was measured using the Beck Anxiety Inventory. Correlations with leptin were conducted using untransformed values. BMI was treated as a continuous variable in these correlations

inflammation, weight gain, and cancer recurrence [37, 38]. Elevated leptin and leptin resistance among obese survivors may contribute to engagement in unhealthy behaviors such as overeating and a sedentary lifestyle. These behaviors increase the likelihood of experiencing long-term health risks throughout survivorship along with continued obesity. Obesity can also increase risk for cardiovascular morbidity among breast cancer survivors [13]. More broadly, leptin signals immune cells to activate, promoting the release of proinflammatory cytokines [38]. Inflammation contributes to tumor initiation, growth, and metastases, ultimately resulting in poorer prognoses, risk for recurrence, and reduced survival among cancer patients [39–41]. Inflammation also has bidirectional associations with both depressive and anxiety symptoms [42, 43]. Importantly, inflammation also contributes to leptin resistance [44, 45]. Future research should seek to understand the interrelationships among inflammation, leptin resistance, and psychological distress such as anxiety or depression. Taken together, our findings therefore highlight the biological underpinnings of how obesity may increase morbidity and mortality among breast cancer survivors.

This study is the first to examine depression and anxiety's associations with leptin among breast cancer survivors. Previous researches testing the influence of psychological factors such as depression and anxiety on leptin remain limited. Generally, depression and anxiety are associated with low leptin among physically healthy adults, but many studies control for BMI and do not test differences between obese and non-obese people despite research suggesting leptin functions differently in obese individuals [25–27]. Women's leptin levels in this study were higher than previous research among physically healthy women [46]. Although research on normal levels of leptin is sparse, some research suggests that leptin is higher among women with breast cancer compared to physically healthy controls, likely accounting for the higher levels found among the survivors in this study [19]. High leptin promotes tumor development and growth along with cardiovascular morbidity among breast cancer survivors, contributing to increased risk for comorbid conditions, reduced quality of life, and mortality [14–18].

Our study extends findings where depressive symptoms predicted lower and higher leptin among normal weight and

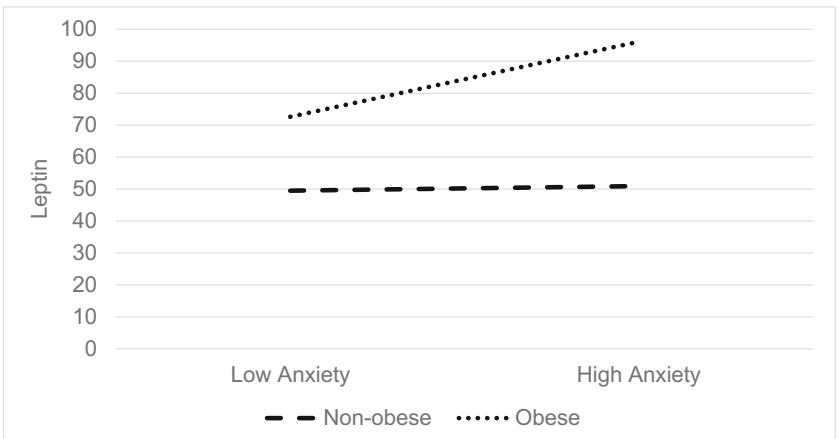

Fig. 1 The Interaction between obesity status (obese vs. non-obese) and anxiety. Within-person fluctuations (e.g., how a woman's anxiety differed from her own average) in BAI are represented in this graph. Leptin levels were significantly higher among obese survivors compared no non-obese survivors regardless of their anxiety ($p < .01$). Untransformed leptin values were used in this figure and values are measured as ng/ml

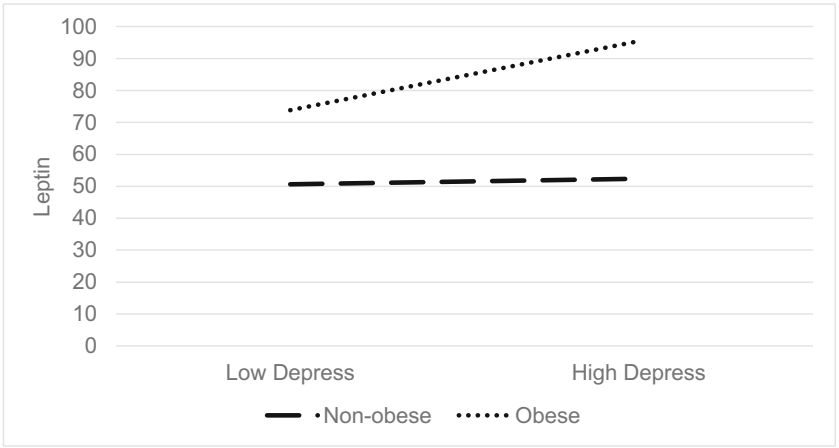

Fig. 2 The interaction between obesity status (obese vs. non-obese) and depression. Within-person fluctuations (e.g., how a woman's depression differed from her own average) in CES-D are represented in this graph. Leptin levels were significantly higher among obese survivors compared no non-obese survivors regardless of their depression ($p < .01$). Untransformed leptin values were used in this figure and values are measured as ng/ml

overweight adults with diabetes, respectively [28]. Breast cancer survivors experience increased risk for depression and anxiety, both of which contribute to significant downstream health consequences including obesity [1]. These results underscore the need for screening and treating depression and anxiety in breast cancer survivors, in line with recommendations from the American Society of Clinical Oncology and accreditation standards for cancer facilities set forth by the American College of Surgeons Commission on Cancer [47, 48]. Understanding psychological pathways that may enhance or exacerbate obesity and its health risks in survivors provides novel information regarding potential preventative physical and psychological interventions.

This study had several strengths. First, this study's design allowed us to test how depression, anxiety, and leptin changed from diagnosis to 18 months after treatment. Our longitudinal design provided a way to examine both within- and between-person changes in anxiety and depression. Previous research is mixed on whether leptin is typically higher or lower in breast cancer, possibly due to the role of intervening factors such as cancer stage and menopause status [19, 49, 50]. Depression and anxiety in this study were linked to leptin after adjusting for age, physical comorbidities, menopause status, cancer stage, sleep, and treatment. Limitations include the fact that the women were not particularly diverse in terms of race and ethnicity. The breast cancer survivors in this study endorsed relatively low rates of depressive and anxiety symptoms, and these results therefore may not be generalizable to women with diagnosable depressive and anxiety disorders. This study also assessed fasting leptin rather than postprandial changes in leptin, an important arena for future research. Furthermore, this study does not allow inferences about how depression and anxiety might be related to leptin among women without a breast cancer history. The behavioral and physiological mechanisms that may drive the relationship between psychological health and leptin should be explored in future research.

In sum, this longitudinal study demonstrated that obese survivors' leptin was higher at visits where she had more anxiety and depressive symptoms than what was usual for her, compared to visits when they had fewer symptoms than usual. These data suggest that leptin, a hormone involved in appetite regulation and inflammation, may be one factor that links depressive and anxiety symptoms to weight gain and obesity. Within-person fluctuations in depression and anxiety influenced leptin among women who are already obese, potentially increasing risk for related diseases throughout survivorship. These novel data provide another perspective on how psychological functioning influences appetitive hormones, thus highlighting important pathways to improve long-term physical health.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of The Ohio State University's institutional research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

References

1. Carreira H, et al. Associations between breast cancer survivorship and adverse mental health outcomes: a systematic review. J Nat Cancer Inst. 2018;110(12):1311–27.
2. Di Angelantonio E, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet. 2016;388(10046):776–86.

3. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat. 2010;123(3):627–35.
4. Chan D, et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol. 2014;25(10):1901–14.
5. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev. 2007;8(1):21–34.
6. Allison MB, Myers M. Connecting leptin signaling to biological function. J Endocrinol. 2014;223(1):T25–35.
7. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000;404(6778):661–71.
8. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med. 1996;334(5):292–5.
9. Dallner OS, Marinis JM, Lu YH, Birsoy K, Werner E, Fayzikhodjaeva G, et al. Dysregulation of a long noncoding RNA reduces leptin leading to a leptin-responsive form of obesity. Nat Med. 2019;25(3):507–16.
10. Jung CH, Kim M-S. Molecular mechanisms of central leptin resistance in obesity. Arch Pharm Res. 2013;36(2):201–7.
11. Myers MG Jr, Heymsfield SB, Haft C, Kahn BB, Laughlin M, Leibel RL, et al. Defining clinical leptin resistance-challenges and opportunities. Cell Metab. 2012;15(2):150–6.
12. Toh YL, Tan CJ, Yeo AHL, Shwe M, Ho HK, Gan YX, et al. Association of plasma leptin, pro-inflammatory adipokines and cancer-related fatigue in early-stage breast cancer patients: a prospective cohort study. J Cell Mol Med. 2019;23(6):4281–9.
13. Blair CK, et al. Obesity and survival among a cohort of breast cancer patients is partially mediated by tumor characteristics. NPJ Breast Cancer. 2019;5(1):1–7.
14. Dieudonne M-N, Machinal-Quelin F, Serazin-Leroy V, Leneveu MC, Pecquery R, Giudicelli Y. Leptin mediates a proliferative response in human MCF7 breast cancer cells. Biochem Biophys Res Commun. 2002;293(1):622–8.
15. Hu X, et al. Leptin—a growth factor in normal and malignant breast cells and for normal mammary gland development. J Natl Cancer Inst. 2002;94(22):1704–11.
16. Andò S, et al. Obesity, leptin and breast cancer: epidemiological evidence and proposed mechanisms. Cancers. 2019;11(1):1–27.
17. Lorincz A, Sukumar S. Molecular links between obesity and breast cancer. Endocr Relat Cancer. 2006;13(2):279–92.
18. Garofalo C, Surmacz E. Leptin and cancer. J Cell Physiol. 2006;207(1):12–22.
19. Wu M, et al. Circulating levels of leptin, adiposity and breast cancer risk. Br J Cancer. 2009;100(4):578–82.
20. Jim HS, Andrykowski MA, Munster PN, Jacobsen PB. Physical symptoms/side effects during breast cancer treatment predict post-treatment distress. Ann Behav Med. 2007;34(2):200–8.
21. Ng CG, Mohamed S, Kaur K, Sulaiman AH, Zainal NZ, Taib NA, et al. Perceived distress and its association with depression and anxiety in breast cancer patients. PLoS One. 2017;12(3):e0172975.
22. Walker J, Hansen CH, Martin P, Symeonides S, Ramessur R, Murray G, et al. Prevalence, associations, and adequacy of treatment of major depression in patients with cancer: a cross-sectional analysis of routinely collected clinical data. Lancet Psychiatry. 2014;1(5):343–50.
23. Pitman A, et al. Depression and anxiety in patients with cancer. Bmj. 2018;361:1–6.
24. Finger BC, Dinan TG, Cryan JF. Leptin-deficient mice retain normal appetitive spatial learning yet exhibit marked increases in anxiety-related behaviours. Psychopharmacology. 2010;210(4):559–68.
25. Lawson EA, Miller KK, Blum JI, Meenaghan E, Misra M, Eddy KT, et al. Leptin levels are associated with decreased depressive symptoms in women across the weight spectrum, independent of body fat. Clin Endocrinol. 2012;76(4):520–5.
26. Yoshida-Komiya H, Takano K, Fujimori K, Niwa SI. Plasma levels of leptin in reproductive-aged women with mild depressive and anxious states. Psychiatry Clin Neurosci. 2014;68(7):574–81.
27. Masdrakis VG, Papageorgiou C, Markianos M. Associations of plasma leptin to clinical manifestations in reproductive aged female patients with panic disorder. Psychiatry Res. 2017;255:161–6.
28. Haleem DJ, Sheikh S, Fawad A, Haleem MA. Fasting leptin and glucose in normal weight, over weight and obese men and women diabetes patients with and without clinical depression. Metab Brain Dis. 2017;32(3):757–64.
29. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988;56(6):893.
30. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977;1(3):385–401.
31. Simon GE, von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, et al. Association between obesity and psychiatric disorders in the US adult population. Arch Gen Psychiatry. 2006;63(7):824–30.
32. Andrykowski MA, Donovan KA, Laronga C, Jacobsen PB. Prevalence, predictors, and characteristics of off-treatment fatigue in breast cancer survivors. Cancer. 2010;116(24):5740–8.
33. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47(11):1245–51.
34. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001;2(4):297–307.
35. Brauer M, Curtin JJ. Linear mixed-effects models and the analysis of nonindependent data: a unified framework to analyze categorical and continuous independent variables that vary within-subjects and/or within-items. Psychol Methods. 2018;23(3):389–411.
36. Shrout MR, Renna ME, Madison AA, Alfano CM, Povoski SP, Lipari AM, et al. Relationship satisfaction predicts lower stress and inflammation in breast cancer survivors: a longitudinal study of within-person and between-person effects. Psychoneuroendocrinology. 2020;118:104708.
37. Rose DP, Gilhooly EM, Nixon DW. Adverse effects of obesity on breast cancer prognosis, and the biological actions of leptin. Int J Oncol. 2002;21(6):1285–92.
38. Naylor C, Petri WA Jr. Leptin regulation of immune responses. Trends Mol Med. 2016;22(2):88–98.
39. Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G. Inflammation and cancer: how hot is the link? Biochem Pharmacol. 2006;72(11):1605–21.
40. Smyth MJ, Cretney E, Kershaw MH, Hayakawa Y. Cytokines in cancer immunity and immunotherapy. Immunol Rev. 2004;202(1):275–93.
41. Thaker PH, Han LY, Kamat AA, Arevalo JM, Takahashi R, Lu C, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nat Med. 2006;12(8):939–44.
42. Kiecolt-Glaser JK, Derry HM, Fagundes CP. Inflammation: depression fans the flames and feasts on the heat. Am J Psychiatr. 2015;172(11):1075–91.
43. Renna ME, O'Toole MS, Spaeth PE, Lekander M, Mennin DS. The association between anxiety, traumatic stress, and obsessive–compulsive disorders and chronic inflammation: a systematic review and meta-analysis. Depress Anxiety. 2018;35(11):1081–94.
44. Sáinz N, Barrenetxe J, Moreno-Aliaga MJ, Martínez JA. Leptin resistance and diet-induced obesity: central and peripheral actions of leptin. Metabolism. 2015;64(1):35–46.

45. Leon-Cabrera S, et al. Hyperleptinemia is associated with parameters of low-grade systemic inflammation and metabolic dysfunction in obese human beings. Front Integr Neurosci. 2013;7:62.
46. Jaremka, L.M., et al., Interpersonal stressors predict ghrelin and leptin levels in women. 2014. 48: p. 178–188.
47. CoC. Optimal Resources for Cancer Care (2020 Standards). 2019 [cited 2020 04/24/2020]; Available from: https://www.facs.org/-/media/files/quality-programs/cancer/coc/optimal_resources_for_cancer_care_2020_standards.ashx. Accessed 15 July 2020.
48. Andersen BL, DeRubeis R, Berman BS, Gruman J, Champion VL, Massie MJ, et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol. 2014;32(15):1605–19.
49. Coskun U, et al. Serum leptin, prolactin and vascular endothelial growth factor (VEGF) levels in patients with breast cancer. Neoplasma. 2003;50(1):41–6.
50. Stattin P, Söderberg S, Olsson T, Hallmans G, Lenner P, Biessy C, et al. Plasma leptin and breast cancer risk: a prospective study in northern Sweden. Breast Cancer Res Treat. 2004;86(3):191–6.