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Low social and family well-being is associated with greater RAGE ligand s100A8/A9 and interleukin-1 beta levels in metastatic breast cancer patients

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ABSTRACT

Greater inflammatory signaling has been shown to promote breast cancer disease progression and poorer clinical outcomes. Lower social support and social well-being have been related to greater inflammatory signaling and poorer clinical outcomes in women with non-metastatic breast cancer, and this appears to be independent of depression. However, little is known about these associations in women with metastatic disease. s100A8/A9 and interleukin 1 beta (IL-1β) proteins are widely studied in breast cancer and are considered as biomarkers of cancer progression or as having a causal role in carcinogenesis and cancer progression and metastasis via inflammatory signaling. The aim of this study was to examine the associations between less social/family well-being (SWB) and S100A8/A9 and IL-1β levels in women diagnosed with metastatic breast cancer. Sixty women (Mean age 58.95 ± 1.49) with a diagnosis of metastatic breast cancer participated in the study. The Functional Assessment of Cancer Therapy (FACT) social and family well-being (SWB) subscale and the Hospital Anxiety Depression Scale (HADS) were administered to patients undergoing a first- or second-line endocrine or oral chemotherapy treatment and who were not experiencing brain metastasis or visceral crisis. Salivary s100A8/A9 and IL-1β levels were assessed at 5PM on two consecutive days and averaged. Multiple regression tested the independent contribution of SWB on s100 A8/A9 and IL-1b while controlling for depression. Lower levels of SWB were associated with greater S100A8/A9 ($\beta = -0.345$, $p = 0.007$) and IL-1β ($\beta = -0.286$, $p = 0.027$) levels and these associations remained significant after controlling for depression. This work provides new evidence for the role of decreased SWB and greater s100A8/A9 and IL-1b levels in patients diagnosed with metastatic breast cancer. Psychosocial interventions that promote social support and positive social interactions through interpersonal skills may help metastatic breast cancer patients to improve their SWB. This may have salutary effects on cancer-promoting processes, which could provide psychological and physical health benefits.

The quality and quantity of emotional support received from friends and family affect a range of health outcomes including mental and physical health and mortality risk (Umberson and Karas Montez, 2010). At the biological level social support affects gene expression, intracellular signaling mechanisms and inflammatory biomarkers (Kiecolt-Glaser et al., 2010). A large study in Finland found that cancer patients diagnosed in 2000–2017 who lived alone had an 11%–80% statistically significantly increased case-fatality and all-cause mortality after cancer diagnosis. (Elovainio et al., 2021). In another study, patients with diverse types of cancer who reported lower social support satisfaction presented higher levels of C-reactive protein, IL-6, and TNF-α and had greater risk of mortality over time (Boen et al., 2018). Thus, a mechanism through which social isolation, lack of social support and high social strain may affect increased case fatality-risk and all-cause mortality is inflammation.

Lower levels of social/family wellbeing have been related to greater leukocyte pro-inflammatory and pro-metastatic gene expression in women with breast cancer (Jutagir et al., 2017) and with greater inflammatory cell signaling in women with ovarian cancer (Lutgendorf et al., 2002). Importantly, lower social support has also been associated with shorter survival time in ovarian cancer patients (Lutgendorf et al., 2012). More recently, socially isolated patients with primary breast tumors were shown to have multiple prometastatic molecular alterations

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such as upregulation of genes involved in epithelial-mesenchymal transition (EMT) and alternatively activated or M2 macrophage polarization and increased density of lymphatic vessels in primary tumor and its microenvironment (Bower et al., 2018). Most of these associations between poor social support, cancer-promoting biological processes and clinical outcomes have been documented in patients with non-metastatic disease. It is however plausible that biological correlates of low social support may mediate its effects on poorer disease outcomes in metastatic breast cancer specifically by altering circulating proteins known to promote cancer progression. Two such proteins are S100A8/A9 and Interleukin 1 beta (IL-1β).

S100/A8 and S100/A9 are Ca2+ binding proteins belonging to the S100 family and frequently exist in the form of heterodimer called calprotectin (Pruenster et al., 2016). This heterodimer is a ligand for the receptor for advanced glycation end products (RAGE), activating nuclear factor kappa B (NF-κB), and stimulating the production of pro-inflammatory cytokines leading to the migration of neutrophils, monocytes, and macrophages (Gebhardt et al., 2008). In breast cancer, S100A8 and S100A9 have a role in tumor microenvironment, are considered crucial factors for establishing the pre-metastatic niche (i.e., favorable microenvironment created by primary tumors in secondary organs and tissue sites for subsequent metastases) at multiple organ sites and also mediate chemoresistance, tumor progression and shorter survival (Acharyya et al., 2012; Bresnick et al., 2015; Cancemi et al., 2018; Li et al., 2014; McKiernan et al., 2011; Yin et al., 2013). Moreover, s100/A8 and A9 promote drug resistance and predict poor disease-free survival in adjuvant endocrine therapy-treated patients (Allgöwer et al., 2020; Bresnick et al., 2015; Donato et al., 2012; Hua et al., 2020; Rafii and Lyden, 2006). Another circulating protein relevant in breast cancer is IL-1β, a member of the interleukin 1 family of cytokines. IL-1β is an important mediator of the inflammatory response, and is involved in a variety of other cellular activities, and may promote both tumor induction and tumor propagation (Bent et al., 2018; Dinarello, 2014). The functions of s100A8/A9 and IL-1b proteins in cancer-related inflammation are complex and they are considered either as biomarkers of cancer progression or as having a causal role in carcinogenesis and cancer progression and metastasis (Bresnick et al., 2015; Holen et al., 2016; Mantovani et al., 2018; Ridker et al., 2017; Yin et al., 2013). Importantly, s100 proteins and IL-1β are viewed as attractive targets for pharmacologic intervention aiming to control cancer progression and severity through the blockage or modulation of their signaling (Bresnick, 2018; Hudson and Lippman, 2018; Kaplanov et al., 2019; Ridker et al., 2017).

There is growing evidence that psychosocial factors may contribute to levels of both IL-1β and s100's. IL-1β is increased by psychological stress (Brydon et al., 2005). A study, based on a preclinical (mouse) model, reported that a rapid release of s100A8/A9 can be induced by stress hormones such as epinephrine, norepinephrine, cortisol and serotonin (Perego et al., 2020). As noted previously, lower levels of social support are related to greater inflammation and poorer disease outcomes in breast cancer patients and it is reasonable that these effects may be explained, in part by greater levels of s100s and IL-1β. Because this literature is focused on breast cancer patients with non-metastatic disease we know little about how social support deficits relate to these markers in women with metastatic. The aim of the current study is to examine the associations between S100A8/A9 and IL-1β levels and social/family well-being in women diagnosed with metastatic breast cancer. Specifically, we hypothesized that lower levels of social and family well-being are associated with higher S100A8/A9 and IL-1β levels. Since other psychological factors (e.g., depression) have also been related to lower social support in the one hand (Bener et al., 2017; Wondimagegnehu et al., 2019) and greater levels of inflammatory markers on the other (Bouchard et al., 2016), in breast cancer patients, we sought to examine the independent contribution of lower social support to s100A8/A9 and IL-1β while controlling for concurrent depression levels.

Table 1
Characteristics of the sample (n = 60).

Variable	Mean ± SD or %	Median	Min-Max
Age, yrs	58.95 ± 1.49	59	43–84
Ethnicity, % White	100		
Marital status, %			
Never married	8.3		
Married	70		
Divorced	15		
Widowed	6.7		
Education, yrs[a]	15.27 ± .41	17	9–20
Time since breast cancer diagnosis, months	95.35 ± 13.24	56.5	5–372
Time since metastasis diagnosis, months	20.89 ± 2.7	14	1–99
Depressive symptoms score:			
HADS-D	5.97 ± .63	6	0–19
Social and Family Well-Being Score:			
FACT- SWB	19.6 ± .63	19.83	11–28
Stage of disease (%):			
IV	100		
Hormone (ER/PR) receptor status (%):			
Positive	100		
Negative	0		
HER2 Status (%):			
Positive	0		
S100A8/A9 mean level (ng/mL)[b]	8444.2 ± 14894.05	3853.5	228.7–101283
IL1-β level (ng/mL)[b]	242.5 ± 293.24	138.9	4.23–1553.97

Abbreviations·
[a] Values indicate the years of full-time education completed.
[b] Raw values.

1. Methods

1.1. Subjects characteristics, recruitment and inclusion/exclusion criteria

Women diagnosed with metastatic breast cancer receiving treatment at the Breast Unit of the Champalimaud Clinical Center in Lisbon were invited to participate in the study by an oncologist. Patients were consented and recruited continuously until the desired sample size (N = 65) was achieved. Five patients were excluded during the study, 1 due to quick deterioration of their health condition and the others because they did not complete the questionnaires or did not collect their saliva for biomarker analyses. The total number of patients used in study analyses were N = 60. Table 1 presents the clinical and demographic characteristics of the patients.

Study inclusion criteria were: 1) women age >18 years; 2) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or1[1]; 3) the presence of metastatic breast cancer not amenable to curative treatment by surgery or radiotherapy; 4) having positive ER/PR receptors and HER2-negative breast cancer; 5) undergoing treatment with endocrine therapy (i.e., tamoxifen or aromatase inhibitors) or oral chemotherapy (vinorelbine, capecitabine, or metronomic cyclophosphamide/methotrexate) or targeted therapy; 6) receipt of first-line or second-line of treatment. These criteria were included because patients who are receiving the first or second line of treatment have good performance status, absence of visceral crisis, reduced burden of disease and allowed us to have a homogeneous sample regarding disease condition and severity, functionality, and treatment exposure; 7) adequate bone marrow, coagulation, liver, and renal function (assessed by physician at the clinical visits). Patients were not eligible to participate in the study if

[1] The ECOG scale is used to assess performance status and for prognosis assessment and ability to tolerate chemotherapy; an ECOG score of 0 indicates fully active, no performance restrictions; ECOG 1, strenuous physical activity restricted, fully ambulatory and able to perform light work; ECOG 2, capable of all self-care but unable to perform any work activities up to approximately >50% of waking hours (Oken et al., 1982).

they had any of the following: 1) the presence of brain or other CNS metastases, confirmed by a PET scan; 2) receipt of radiation therapy to the brain or skull lesions; 3) the presence of neurodegenerative or neurologic disease; 4) current treatment with corticosteroids or intravenous chemotherapy; and 5) HER2-positive breast cancer, the presence of visceral crisis, and/or significant burden of disease.

1.2. Procedure

Eligible patients were informed about the study and invited to participate by the oncologist. Those who accepted signed an informed consent form. Ethical approval for this study was obtained from the Ethics Committee of Champalimaud Foundation (DistressBrain RProject, 180718). A psychologist instructed patients on how to complete the questionnaires at home. Patients also received a saliva collection kit and were given oral and written instructions for the collection of their saliva at home. Kits included pre-labeled collection tubes or "salivettes", consisting of a plain cotton swab fitted into a plastic holder. Patients stored their saliva samples in the refrigerator before they returned them to the lab. One day after collecting the saliva, participants completed the questionnaires.

1.3. Psychological assessments

We measured social and family well-being and depression by questionnaires. The Functional Assessment of Cancer Therapy (FACT-G) (Brucker et al., 2005), evaluates quality of life in cancer patients, and one module of this scale comprises the social/family well-being (SWB) subscale which has 7 items, rated on a 5-point Likert scale. This scale measures the perception of emotional support that an individual is receiving from their friends and family members. The scale includes the following items: "I feel close to my friends"; "I get emotional support from my family", "I get support from my friends", "My family has accepted the illness", "I am satisfied with family communication about the illness", "I feel close to my partner (or the person who is my main support)", "I am satisfied with my sex life". Patients reported their perceptions over the past seven days (Score range: 0–28). We used the Portuguese version of SWB subscale, which has a Cronbach's alpha value of 0.82 (Pereira and Santos, 2011). The SWB subscale was previously associated with less inflammatory cell signaling in women diagnosed with ovarian cancer (Lutgendorf et al., 2002) and with less leukocyte pro-inflammatory and pro-metastatic gene expression in women after surgery for breast cancer (Jutagir et al., 2017).We also administered the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) validated for the Portuguese population (Pais-Ribeiro et al., 2007). The HADS has good accuracy in assessing anxiety and depression in cancer patients (Annunziata et al., 2020). While the HADS is a 14-item measure designed to assess anxiety and depression symptoms the present study focused only on the seven items for depression (HADS-D). Each item is endorsed on a Likert-type scale (0–3) and the score obtained ranges from 0 to 21. The Portuguese version has good internal consistency with Cronbach's alpha of 0.81 for the HADS-D.

1.4. Biomarker measurement

The measurement of S100 proteins and IL-1β in saliva has been considered a valid and reliable method (Idris et al., 2015; Janigro et al., 2020; Jonasson et al., 2017; Karna et al., 2019; Spiekermann et al., 2017) and IL-1β is more detectable in saliva than in blood serum (Idris et al., 2015). In the present study, unstimulated whole saliva was self-collected by each patient over 2 consecutive days at 5pm with untreated Salivettes®, as described by the manufacturer (Sarstedt AG & Co. KG, 51588 Nümbrecht, Germany). Saliva was collected at this time to minimize the impact of diurnal fluctuations. Salivary S100A8/A9 and IL-1β levels were calculated averaging the value of each day. Saliva samples were aliquoted and stored at −80 °C until analysis. S100A8/A9 heterodimer concentrations were measured with a sandwich enzyme-linked immunosorbent assay (ELISA) for human S100A8/A9, following the manufacturer's instructions (R & D Systems, Minneapolis, USA). The minimum detectable dose (MDD) of human S100A8/A9 heterodimer ranges from 0.005 to 0.215 ng/mL. The sensitivity of the assay is 0.086 ng/mL (mean MDD). Intraclass correlation coefficient (ICC) were calculated for the two s100A8/A9 measurements, based on absolute-agreement, 2-way mixed-effects model. ICC = 0.429 ($p < 0.05$) with 95% confident interval = [0.025; 0.665]. Test-retest coefficient can be considered fair and is in line with reliability tests of cytokines (Koelman et al., 2019).

IL-β concentrations were measured with a sandwich enzyme-linked immunosorbent assay (ELISA) specifically designed and validated for the quantitative measurement of salivary human IL-1β (Salimetrics LLC, Carlsbad California, USA), following the manufacturer's instructions. The amount of Streptavidin-HRP detected is proportional to the amount of IL-1β present in the sample. The minimal concentration of IL-1β that can be detected is < 0.37 pg/mL. The sensitivity of the assay is 0.6 pg/mL (mean MDD). The Inter-Assay Coefficient of variability was between 3% and 7% and the Intra-Assay Coefficient of variability was between 2% and 3%. ICC were calculated for the two IL-1β measurements, based on absolute-agreement, 2-way mixed-effects model. ICC = 0.756 ($p < 0.05$) with 95% confident interval = [0.587; 0.856].

1.5. Statistical analysis

Statistical analyses were conducted using IBM SPSS version 27 (IBM Corporation). A significance level of 5% for two-tailed tests was set. Prior to analysis, all data were checked for normality and homogeneity of variance using Q-Q plots and boxplots. These procedures indicated that s100A8/A9 and IL-1β data were positively skewed, and the distributions were not normal. Thus, we used a natural log-transformation of s100A8/A9 and IL-1β data to obtain a normal distribution and a linear relationship. After this transformation, we conducted a curve estimation regression procedure which indicated that the relationship between the dependent and independent variables was linear. The variables age, education, time since breast cancer diagnosis, time since metastasis diagnosis and body mass index (BMI) were defined as covariates since they may be related to distress and inflammatory markers (O'Connor et al., 2009). These covariates were also controlled in previous studies relating psychological distress states to immune markers in patients with breast cancer (Blomberg et al., 2009; Bouchard et al., 2016; Jutagir et al., 2017). Pearson correlations were used to evaluate the associations of these covariates with S100A8/A9 and IL-1β. In regression analysis we performed Bias – corrected and accelerated bootstrap confidence intervals (95%) for unstandardized Beta, with 5000 samples. An *apriori* power analysis, using the G*power 3.1 program (Erdfelder et al., 1996), setting a linear multiple regression; a moderate effect size ($f^2 = 0.015$) (Cohen, 1988); an alpha = .05 (two-sided) and a *Beta* = 0.20 (power of .80), indicated that a sample size of 55 would be sufficient. An analysis of missing values indicated that they were missing completely at random (MCAR) and that the percentage of missing data in the total dataset was less than 5%. Scores were imputed using an Expectation-Maximization (EM) procedure (Gold and Bentler, 2000).

2. Results

2.1. Social/family well-being and s100A8/A9

Bivariate Pearson correlation indicated that BMI correlated significantly with S100A8/A9 ($R = 0.293$, $p < 0.05$, two-tailed). Age, education, time since breast cancer diagnosis and time since metastasis diagnosis did not correlate with S100A8/A9. Thus, we included BMI as a covariate in the multivariate model. First, we performed a simple linear regression to relate social/family well-being (SWB subscale scores) to s100A8/A9 levels. Results indicated that SWB was significantly negatively correlated with S100A8/A9 levels. The model was significant,

$F_{(1,58)} = 7.838$ ($p = 0.007$), R^2 change = 0.119, Std ß = −0.345 ($p = 0.007$), unstd ß = −0.107, CI [−0.182, −0.030]. Next, since BMI was associated with greater s100A8/A9 we reran this analysis controlling for BMI. The model was significant $F_{(1,57)} = 5.513$ ($p = 0.007$), R^2 change = 0.162, with SWB significantly associated with S100A8/A9: Std ß = −0.287 ($p = 0.027$), unstd ß = −0.089, CI [−0.166 -0.010]. However, BMI was no longer significantly associated with s100A8/A9: Std ß = −0.216 ($p = 0.093$), unstd ß = −0.054, CI [−0.013,0.129]. Fig. 1 depicts the scatterplot of the simple association between SWB and S100A8/A9. Examination of the scatter plot indicates that the association was not being driven by extreme values.

2.2. Social/family well-being and interleukin 1-beta

Bivariate Pearson correlation indicated that no covariate correlated with IL-1β. Thus, we conducted a simple linear regression model between IL-1β and SWB. The model was significant, $F_{(1,58)} = 5.148$ ($p = 0.027$), R^2 change = 0.082, Std ß = −0.286 ($p = 0.027$), unstd ß = −0.77, CI [−0.131, −0.017]. Fig. 2 depicts the scatterplot of the association between SWB and IL-1β. Examination of the scatter plot indicates that the association was not being driven by extreme values.

2.3. Social/family well-being, s100A8/A9, interleukin 1-beta and depression

A bivariate Pearson correlation indicated that depression (HADS-D score) was significantly positively correlated with s100A8/A9 ($R = 0.28$ $p = 0.030$) and negatively correlated with SWB ($R = -0.399$, $p = 0.002$). Thus, we performed a multiple linear regression to examine the association between SWB and s100A8/A9, controlling for depression. The model was significant $F_{(1,57)} = 4.765$ ($p = 0.012$), R^2 change = 0.143, but only SWB was significantly associated with S100A8/A9: Std ß = −0.277 ($p = 0.043$), unstd ß = −0.086, CI [−0.167, −0.003]. The association of depression with S100A8/A9 was no longer significant once we controlled for SWB: Std β = 0.170 ($p = 0.210$), unstd β = 0.045, CI [−0.028, 0.127].

A bivariate Pearson correlation indicated that IL-1β was not significantly correlated with depression (HADS-D score) ($R = 0.024$, $p > 0.05$) thus, we did not test for multilinear effects of SWB and depression on IL1-β.

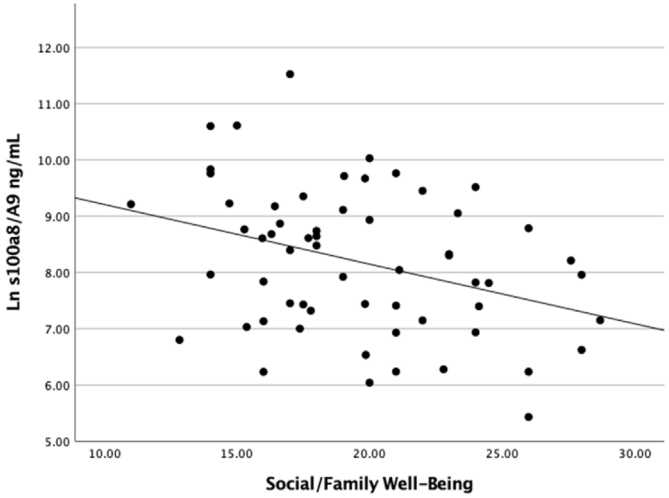

Fig. 1. Scatter plot and regression line for association between social/family well-being and natural log-transformed salivary S100A8/A9 levels in women with metastatic breast cancer. Considering Cohen's moderate effect size threshold for Pearson correlation coefficients (r > 0.3) (Cohen, 1988), the differences in s100A8/A9 levels for high and low social/family well-being are clinically significant (The Std ß = −0.345 is equivalent to the Pearson correlation coefficient when there is a single predictor variable).

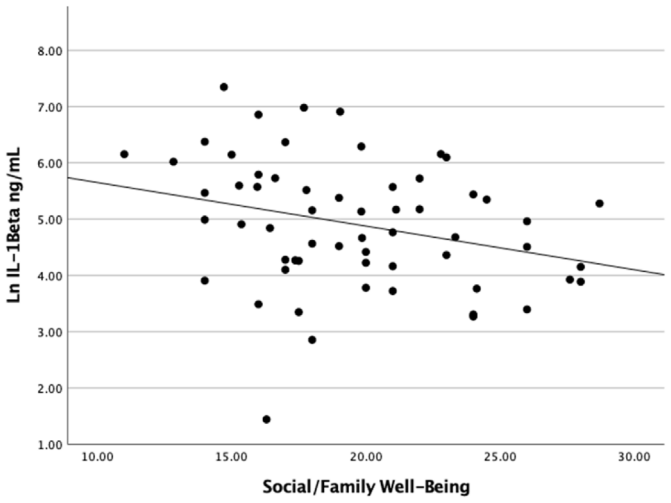

Fig. 2. Scatter plot and regression line for association between social/family well-being and natural log-transformed salivary IL-1β levels in women with metastatic breast cancer. Considering Cohen's moderate effect size threshold for Pearson correlation coefficients (r > 0.3) (Cohen, 1988), the differences in IL-1β levels levels for high and low social/family well-being are not clinically significant (The Std ß = −0.286 is equivalent to the Pearson correlation coefficient when there is a single predictor variable).

3. Discussion

The results of this study confirmed our hypothesis that lower levels of social/family well-being (SWB) were associated higher S100A8/A9 and IL-1β levels among women with metastatic breast cancer. As far as we know it is the first study that examined the association of SWB with s100A8/A9. Also, these findings add evidence about the role of low SWB in inflammation in breast cancer and extend these associations for the first time to women with metastatic disease. These results mirror other reported associations between lower SWB and greater leukocyte pro-inflammatory and pro-metastatic gene expression in patients with non-metastatic breast cancer (Jutagir et al., 2017) and are in line with studies showing that low social support relates to inflammatory processes in patients with other cancers (Cohen et al., 2012; Lutgendorf et al., 2008). While depressive symptoms were significantly associated with greater S100A8/A9 and lower SWB, the association of depressive symptoms with S100A8/A9 was no longer significant once we controlled for SWB.

Social adversity may have a powerful influence on physiology through neuroendocrine, autonomic and immune pathways (Davidson and McEwen, 2012; McEwen, 2012) and, particularly, in promoting systemic chronic inflammation, which underlies several diseases (Furman et al., 2019). In line with these findings, studies with patients with metastatic breast cancer and other metastatic cancers reported that low social support is related to poorer survival (Cohen et al., 2012; Giese--Davis et al., 2011; Lutgendorf et al., 2012). Elevations in S100 proteins have been associated with tumor progression and shorter survival in breast cancer patients (Cancemi et al., 2018; Li et al., 2014; McKiernan et al., 2011). Thus, an important area for future research is to examine how alterations in SWB may modulate pro-inflammatory s100 proteins to influence cancer prognosis and survival. Psychosocial interventions that promote social support, assertive communication, and positive social interactions may help metastatic breast cancer patients to improve a sense of SWB, reduce pro-inflammatory processes and improve clinical health outcomes such as survival. One randomized controlled trial (RCT) showed that a psychosocial intervention teaching cognitive and interpersonal coping skills improved 11-year disease-free survival in breast cancer patients, effects that were accounted for, in part, by reductions in a leukocyte pro-inflammatory gene expression profile (Antoni et al.,

2016) that was also associated with low SWB in breast cancer patients (Jutagir et al., 2017). In another RCT a psychosocial intervention shown to improve survival in women with breast cancer who had already experienced a recurrence (Andersen et al., 2010) may have also improved SWB via the cognitive and interpersonal coping skills taught in the intervention. Together these studies suggest that interventions that provide the skills to improve SWB and other elements of social support in women with breast cancer may decrease the odds of recurrence or improve survival after metastatic spread. Future work should test whether similar interventions can promote long-term survival in the steadily growing population of HR + HER2neu-metastatic breast cancer patients (Lobbezoo et al., 2013). This group of patients with metastatic breast cancer, the sample used in the present study, are being treated successfully with life-extending cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor targeted therapies in combination with anti-hormonal therapies (Cristofanilli et al., 2016; Finn et al., 2016; Tripathy et al., 2018). If such targeted therapies transform metastatic breast cancer into a chronic disease then psychosocial interventions capable of modulating pro-inflammatory and pro-metastatic processes by improving SWB and decreasing other aspects of symptom burden and adversity that may come with these regimens (Oswald et al., 2021) may provide clinical benefits in the future.

While the present findings are provocative some aspects of the study design should be considered when interpreting these results. Study limitations were the use of a cross-sectional design and a convenience sample of patients who were lacking diversity in race/ethnicity and sociodemographic status. These factors acted to limit any causal conclusions and generalizability to other populations beyond well-educated Caucasian patients with HR + Her2neu-metastatic breast cancer. Moreover, although the directionality of association between social adversity and cytokines has been previously established, bidirectional associations could not be ruled out in this cross-sectional study. For example, IL-1β has been reported to induce "sickness behavior" since it can activate the hypothalamic-pituitary-adrenal axis and is a potent regulator of serotonin transporter gene indicating that this interleukin may have a role in the biology of depression (Licinio and Wong, 1999). Besides psychosocial stress, inflammatory diseases can induce depression as well (Grygiel-Górniak et al., 2019). Another facet of sickness behavior may involve social and behavioral withdrawal (Dantzer, 2018; DiSabato et al., 2021) suggesting that social isolation and decreased social interactions may accompany elevations in IL-1β.

Strengths of this study include the recruitment of a homogenous sample of women with a specific type and stage of cancer who had a predefined exposure to different forms of cancer treatments, excluding current treatment with corticosteroids or intravenous chemotherapy. Because of the possibility that variability in treatment regimens could impact our inflammatory markers we selected a sample of metastatic breast cancer patients only receiving first-or second-line treatments restricted to endocrine therapy and oral chemotherapies and excluded cases presenting with brain metastasis or who were using corticoids. While it is infeasible to control for all sources of treatment variability on study outcomes, we believe that this was a reasonable strategy. Moreover, patients that participated in this study are experiencing a stressful time, when social resources, such as social ties and family and friends support may be particularly important (Oswald et al., 2021). In fact, patients with metastatic disease have an enhanced feeling of uncertainty because they are more aware about the incurable nature of their disease and that its evolution is much less predictable (Burnet and Robinson, 2000; Warren, 2010). They also face many challenges such as frequent medical procedures, chronic side effects and numerous practical concerns in daily life, all of which can compound a sense of stress and adversity (Mosher et al., 2013). Another strength refers to the evaluation of a novel marker of inflammation (s100A8/A9) with clinical relevance to breast cancer and finally the focus on metastatic breast cancer, which is an understudied population regarding biobehavioral processes and pathways that can modulate clinical outcomes.

4. Summary

We found that low social/family well-being was related to greater levels of inflammatory biomarkers (s100A8/A9 and IL-1β) in women with HR + Her2Neu-metastatic breast cancer. These findings are in line with a recent review suggesting that changes in the social environment may promote inflammation (Furman et al., 2019). Psychosocial interventions that promote social support, assertive communication, and positive social interactions may help metastatic breast cancer patients to improve their social/family well-being and their ability to request support from other people in their social network. This may reduce pro-inflammatory processes that could influence clinical health outcomes in the understudied but emerging population of women undergoing treatment for metastatic breast cancer.

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Declaration of competing interest

Dr. Antoni discloses that he is a paid consultant for Blue Note Therapeutics, and Atlantis Healthcare, two digital health software companies specializing in developing psychosocial interventions for medical patients. The other authors have no conflicts of interest to declare.

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