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Psychological Features of Breast Cancer in Mexican Women II: The Psychological Network

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Abstract. Breast cancer (BC) is one of the oncological diseases most frequently diagnosed in adult women worldwide. As with other cancer types, BC is thought to emerge after genetically susceptible stem epithelial cells display uncontrolled proliferation after being chronically exposed to stressful environmental conditions that may include altered hormonal profiles, metabolic status and/or surrounding environmental settings. This scenario, nonetheless, fails to recognize the role that psychological factors play on BC origin, progression and outcome. Accordingly, in the preceding work, we present data that supports that some psychological traits may predispose Mexican women to develop BC. In this complementary paper, we now explore the "relative weight" that emotional suppression and repression and stress symptoms have on the likelihood of women developing BC by establishing, through network analyses, the way these psychological traits interact with well accepted BC-risk environmental, genetic and physiological factors. Since in our model nodes represent personality traits and the links among them (i.e. the "activated" psychic pathways), Pearson's correlation analyses were used to evaluate whether healthy networks are different among health-disease states. In addition, in order to study the associations with the clinical factors, an analysis of principal components (PC) and three multivariate models were constructed in order to determine with precision the psychological predictors of BC.

Results show that the psychological traits, as expected, adopt a network organization, in which BC patients had the most disconnected distribution, followed by the Benign Breast Pathology (BBP) group. Breast pathology according to the resulting network seems to disconnect emotions from the stress response. Our results also show that the variance found between groups can only be explained by psychological traits, that is, in this sample only certain psychological traits increase the susceptibility to BC but none of the most recognized clinical factors do.

Keywords: Psychoneuroimmunology, psycho-oncology, personality, suppression of negative emotions, distress

INTRODUCTION

Breast cancer (BC) is a leading cause of death among women worldwide [1]. In Mexico, BC accounts for 14% of cancer-related deaths. In fact, it has been predicted that by the year 2030, nearly

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24,386 worldwide and around 9,778 Mexican women will be diagnosed with and die of BC respectively [2, 3]. Even though, over the past two decades, the medical establishment has made significant therapeutic advances, we believe that our best chance to reduce BC-related deaths in the coming years is to instrument methods aimed at identifying women with increased risk of developing BC. Accordingly, clinical researchers have developed methods that predict the odds of women to developing BC over their lifetime [4–6; e.g., Gail, BOADICEA and Tyrer-Cuzick], based upon information derived from detailed questionnaires on their genetic, reproductive, nutritional, biological and lifestyle backgrounds [2, 7–11]. The predictability achieved by these instruments reaches, at best, forty percent [12]. Hence, 60% of BC susceptible women continue unidentified. In that respect, it has been suggested that the onset and development of BC may be influenced by psychosocial factors due to the lack of emotional response and/or the stress experienced [13–20]. Hence, adding the psychological evaluation of personality variables and stress coping mechanisms to the clinical model -where genetic, reproductive, biological and lifestyle factors would interact- may enhance its predictability power. In fact, it is well known that personality, emotions and stress have a significant impact on genes, hormones and lifestyle [21–23].

Holland and Lewis (2003) consider that people with a type C personality, those who experience painful and negative emotions but outwardly seem calm and are emotionally contained individuals when facing stress (especially with respect to anger), are more susceptible to develop BC [21].

In the emotional containment context, three possible scenarios may explain the links between emotions and disease: 1) Maladaptive reactions may induce excessive physiological activation that, in the long term, could deteriorate the person's health by promoting chronic stress, immune-depression or chronic inflammation [22, 23]; 2) intense, recurrent and chronic maladaptive emotions (e.g., anxiety, sadness-depression, and anger) could develop and consolidate noxious habits (e.g., drug addiction, high carbohydrate diets and sedentarism); 3) negative emotions could also favor diseased states following an emotional deregulation if cognitive assessments of previous stimuli were inadequate or if voluntary emotional suppression was not engaged in a timely manner [24]. Thus, negative emotions might contribute to unfold carcinogenic processes, which in turn could feedback negatively on emotional and behavioral expressiveness.

Also, the idea that stress and cancer are related has been long lasting. The most recognized road is that in which a chronic stress primes the body to develop cancer since it decreases immune surveillance [25]. Studies conducted in both experimental animals and humans show that, under healthy conditions, natural killer cells protect against tumors by inhibiting their growth and reducing their metastatic potential [26, 27]. Chronic stress, however, suppresses natural killer and T cell responses [28], mononuclear cell counts [29] and increases serum levels of the pro-inflammatory interleukins IL-6 and IL-8 [30].

Thus, the psycho-neuro-immune-endocrine model [31] predicts that women with type C personality traits, most importantly emotional suppression, are prone to over-dimensioning environmental challenges, thus leading them to generate allostatic/pantostatic stress loads [17, 32, 33], supported by the chronic activation of hypothalamic-pituitary-adrenal/gonadal axes (HPA/G) [34]. As a result, increased levels of estrogens secreted by the ovaries and by body fat could elevate the risk of developing BC [34]. On the other hand, chronic stress loads could raise prolactin serum concentrations leading to decreased immune surveillance [32, 35–40].

Even with the psycho-neuro-immune-endocrine model that has been postulated, there are few experimental human studies that sustain this approach. In a previous work [41], we produced data supporting that (at least for this sample of Mexican women) low restraint (hold back emotions), low global stress symptomatology, low physical stress symptoms, low restraint-defensiveness composite (retaining emotions without defensiveness to protect oneself) and high distress scores may render women susceptible to develop BC [see also 5, 42], results which coincide with other studies of women from other countries [43–47]. However, unlike other groups of women, Mexican women suppress anxiety more than anger [41]. In addition, when analyzing levels of emotional repression, Mexican women with BC have high levels of distress, low containment and low containment/defensiveness, which place them in a "sensitive" typology rather than a repressive one as previously reported [48–51].

These previous results show new avenues for a more complex, integrative and earliest BC diagnosis method, there are several questions, in particular, those concerning the greater suppression of anxiety and not anger in Mexican women; and also, the lower

levels of stress symptoms founded in BC women. Therefore it would be interesting to study the relationship between the psychological variables and also their interaction with the clinical ones.

This is important since according with the literature cancer results from an altered network of interaction among multiple internal and external variables that takes place at different levels of organization [52–56]. Thus, it is possible that the BC-risk psychological variables could also adopt network topography, that is, a spatial distribution in which the variables (nodes) are linked and adopt clusters rearrangements. Network Analysis (or Social Network Analysis) is a set of mathematical methods used in social psychology, sociology, ethology and anthropology [57–59]. This methodology assumes that the way the members of a group interact with each other affects some important features of the group (such as performance, leadership, work satisfaction, etc.). We suggest that equivalent actors (*i.e.*, psychological features) and equivalent psychological events (*i.e*, distress, emotional suppression, anxiety, etc.), occur in psychological networks and affect the performance of the BC cells (*i.e.,* tissue invasion, metastasis) and of the immune system of the patient who is either dealing successfully or not with BC. Sequential analysis deals with chains of behavior by way of recording the behavior of an animal under specific personal and circumstantial conditions and then, dividing the complete set of behavior types into basic sequential units, or Links, in order to make with them a single filed sequential chain of nodes [57–59].

In this work, we constructed such a network based on the interactions of psychological variables. At the same time, we also assessed associations between psychological, genetic, environmental and lifestyle variables that are assumed to predispose to BC.

METHODOLOGY

Study groups

This study was conducted in 1) women having no signs or symptoms of breast pathology (Healthy: H; $n = 50$; >22 years old), 2) women having Benign Breast Pathologies (BBP; $n = 50$; >30 years old; fibroadenoma (50%), cystic fibrosis (21%) or mastitis (29%) and 3) women that were diagnosed, through mastography or biopsy, with BC ($n = 50$; >30 years old; infiltrating canalicular (94%), lobular (2%), mucinous (2%) or tubular (2%) tumors) after having their psychological profiling done. H, BBP and BC patients were approached and recruited during the first semester of the year 2012; they all were attending the General Hospital of Mexico "Dr. Eduardo Liceaga" at Mexico City for their regular gynecological checkup. During the initial interview, patients were thoroughly informed on the scientific reaching and research methods involved in the protocol. All women participants signed the corresponding informed consent forms. Then, all patients filled the psychological tests and a detailed data sheet where age, weight, family history of cancer, gynecological, obstetrical and reproductive histories as well as the existence of addictions, nutritional regime and physical activity were recorded and taken into consideration when interpreting the results. Women were grouped based upon their age and personality type and then matched with their final diagnosis. The protocol was reviewed and approved by the Ethical Committee for Clinical Research at the General Hospital of Mexico "Dr. Eduardo Liceaga", Secretaría de Salud (DI/12/111/03/064).

Identifying personality traits and stress symptoms

The Courtauld Emotional Control Total Score (CECS)

This instrument evaluates suppression by rating the intensity of the individual's reactions when experiencing negative emotions. CECS was developed to evaluate suppression in BC-diagnosed women by Watson and Greer (1983). It was adapted for native Spanish speaker patients ($N = 175$) by Dura et al. (2010) [60]. The internal consistency of the Spanish version of CECS proved to be statistically satisfactory with *Cronbach's alpha* coefficients reaching 0.86 for anger suppression (A), 0.88 for depression (D) and anxiety (ANX) sub-scales, and 0.95 for the Total Scale [60].

The Weinberger Adjustment Inventory (WAI)

This instrument estimates repression, defensiveness and restraint [49]. WAI was translated to Spanish and adapted and validated for the Mexican population ($N = 452$) by Romo-González et al. [61]. The internal consistency of the WAI Spanish version proved to be statistically satisfactory with *Cronbach's alpha* coefficients reaching 0.89 for self-control, 0.84 for subjective experience of distress, 0.69 for defensiveness and 0.74 for consideration for others [61].

Symptoms of Stress Inventory (ISE)

This instrument estimates distress under the assumption that stress has physical (SPhys), psychological (SPsych) and social (SSoc) manifestations. ISE was designed to assess the frequency of stress symptoms in psychologists (N = 203). The internal consistency of ISE proved to be statistically satisfactory with *Cronbach's alpha* coefficients of 0.93 [62].

Network analysis

We adapted the theoretical model used by the social network analysis to evaluate interactions, first, between psychological variables, and then, among psychological variables with genetic, life style, socio-demographic and biological ones. This methodology's basic premise assumes that the way the network nodes (i.e., variables) interact one another determines the relative weight of each node within the network and thus the network geometry. We then presumed that psychological traits and events and non-psychological variables would interact in particular ways so that node preponderance and network geometry would differ characteristically among H, BBP and BC women. We believe that such geometries might depict the interactions among variables that could predispose epithelial and immunological cells to display or not "BC prone behaviors" (e.g., compromised immune-competence). Furthermore, sequential analyses allowed us to establish the "relative weight" of each node, as well as to define nodes' interaction chains or links in H, BBP and BC women exposed to specific personal and circumstantial conditions [see also 57–59].

The psychological network model was elaborated by assigning a node for each of the 31 psychological variables. Node interactions and interconnectedness were evaluated by using multiple Pearson's correlation analyses. A network model was constructed for H, BBP or BC women. The significance values were obtained after considering Ho as the null hypothesis in which true correlations equaled zero. Based on the hypothesis-testing algorithm, the testing value was estimated as:

$$t = \frac{r\sqrt{n-2}}{\sqrt{1-r^2}}$$

Where, r is the Pearson's Correlation Coefficient and n is the number of sample observations. Finally, the decisions rule establishes that if $|t| > {t_{\alpha/2}}^{n-2}$, where ${t_{\alpha/2}}^{n-2}$ is the t distribution value with probability $a/2$ and $n-2$ degrees of freedom, thus, the conclusion is the rejection of the null hypothesis, which means that the correlation between two variables is significantly different from zero and it can be considered statistically significant. In terms of probability, the p-values can be obtained by the probability calculation of t (p-*value*), based on the t distribution and the decisions rule indicates that if $p - value < a/2$ then the null hypothesis should be rejected [63].

To create the H, BBP and BC psychological networks, the correlation matrix (R) from k group was transformed into a Binary matrix (B), where $k = 1, 2, 3$. The transformation indicates that if $r_{i,j}$ (the Pearson's Correlation Coefficient between variable i and variable j with $i \neq j$) was considered statistically significant, then, $b_{i,j} = 1$, if the opposite occurs then $b_{i,j} = 0$. In this way, the number of links was given by the number of the ones in B, which means the number of significant Pearson Correlations found in the k group.

Subsequently, if Pearson's Correlations were statistically significant, we turned to plotted them using UCINET 6 for Windows software [64]. UCINET is an independent platform- application designed for social network analysis, sociometry and sequential analysis. UCINET allows the user to create, edit, analyze, store and visualize Networks.

Statistical differences in the number of nodes and links between groups were estimated through Kruskall-Wallis' tests. Differences of the intensity of the Networks' Connectivity among the groups of women were evaluated by estimating the number of significant correlations in k group denoted by N_k. Then, the expected value of all the significant correlations in the k group was calculated by the following relation:

$$M_k = \frac{\sum_{i=1}^{m} r_{i,k}}{m}$$

Where $r_{i,k}$ represented the significant correlation i of the group k. Finally, the connection intensity (I_i) was calculated by:

$$I_k = M_k * N_k$$

As it can be inferred, this last equation indicates the expected value of links in a given k group, based on the values of inter-nodes Pearson's Correlations.

In addition, disconnected nodes were identified using the following algorithm using Excel templates:

if (a==1 && b==0) output = 2
else if (a==0 && b==1) output = 1
else if (a==1 && b==1) output = 0
else (a==0 && b==0) output = 0

Values (1,0) assigned to "a" and "b" correspond to link presence (1) or link absence (0) between the matrix compared (i.e., H vs BBP; H vs BC or BBP vs BC). All matrices were studied to identify whether or not they had an output value = 2. This value denoted the existence of a lost connection. Once all of the nodes with lost connections were identified, a table of disconnections by Node was constructed.

Finally, principal component (PC) analyses were conducted to evaluate how much of the sample variance is explained by psychological variables, non-psychological variables or by the interaction of both in H, BBP and BC women [65]. Three multivariate models were assessed to identify the psychological predictors of BC. In the first model, the BC group was compared against the BBP group. In the second and third models, H women were confronted against BBP or BC patients, respectively.

RESULTS

The organization of the psychological network differs among H, BBP and BC women

The organization of the networks representing H, BBP and BC women are shown in Fig. 1 and in Table 1 shown the networks properties per group, respectively. Even though the total number of links, the average correlation magnitude and the connection intensity of links was similar among groups (Table 1), the overall network connectivity was found decreased in BC women as compared with those representing H or BBP women. The network spatial arrangement also differed significantly among groups (Fig. 1). As an example, whereas a homogeneous 25-node cluster predominated in the H women network, BBP and BC women networks feature two distant clusters each formed by nodes having different relative weights. This is particularly notorious in BC patients in whom low Global symptoms of stress (SGl) and low Social symptoms of stress (SSl) nodes dominate, by far, the entire network.

Network theory predicts that a limited number of connected nodes called "hubs" mediate the rearrangement of a system. In that respect, it is worth noting that the hub with the most sociometric degree in H (17 links) and BBP (13 links) women was high Global symptoms of stress (SGh), while in the case of BC (17 links) was SG1. Therefore, it might be that a poor perception of stress symptoms predisposes individuals to BC.

Besides the above findings, women with BC showed decreased connectivity in hubs having 9 to 12 links and increased connectivity in those having 5 to 8 links as compared with H and BBP women (Fig. 2). In consonance, the average Magnitude of significant correlations (M), the connection intensity (I = NxM) and the intensity ranking order (R) of the most connected hubs became reorganized in BC patients. Indeed, even though there are hubs shared by women of the three groups (Table 2), other connected nodes are somewhat specific to women with breast pathology, specifically, low Global symptoms of stress (SGl) and low Physical symptoms of stress (SFl), or of women with BC, high Restraint-Defensiveness composition (RDh) and low Restrain-Defensiveness composition (RDl). Interestingly, in H women RDh and RDl are located peripherally to the main cluster, whereas in BC women these nodes are located at the core of one of the clusters (Fig. 1). Hub/node reorganization within the networks of different groups is not only seen in terms of their spatial distribution. The degree of connectivity also differs among groups. For instance, high Depression Suppression (Dh) and low Depression Suppression (Dl), nodes that rank 3 and 8 in H women are two of the most disconnected nodes in BBP and BC (Table 3). Thus, BC is associated with a reorganization of the psychological network.

Psychological features have a preeminent organizational action on network structure

We conducted PC analyses to explore the interaction of the psychological variables with lifestyle, genetic, hormonal and environmental variables within the context of the network. The saturation factor indicated that 10 out of 48 variables concentrate the highest linear combination scores, in which we considered the variables that had a value greater than 0.7, both positive and negative, in the first two components (each one explains at least 10% of the variance, the other factors were less than 10%); these variables accounted for 24% of the total variation. More specifically PC1, representing low Physical symptoms of stress (SFl), high Psychological symptoms of stress (SPh), low Psychological symptoms of stress (SPl), high Social symptoms of stress (SSh), low Social symptoms of stress (SSl), high Global symptoms of stress (SGh) and low Global symptoms of stress (SGl), accounted for 14% of the variance, whereas PC2, representing high Depression Suppression (Dh), high Suppression (Sh) and low Suppression (Sl), explained 10% of the

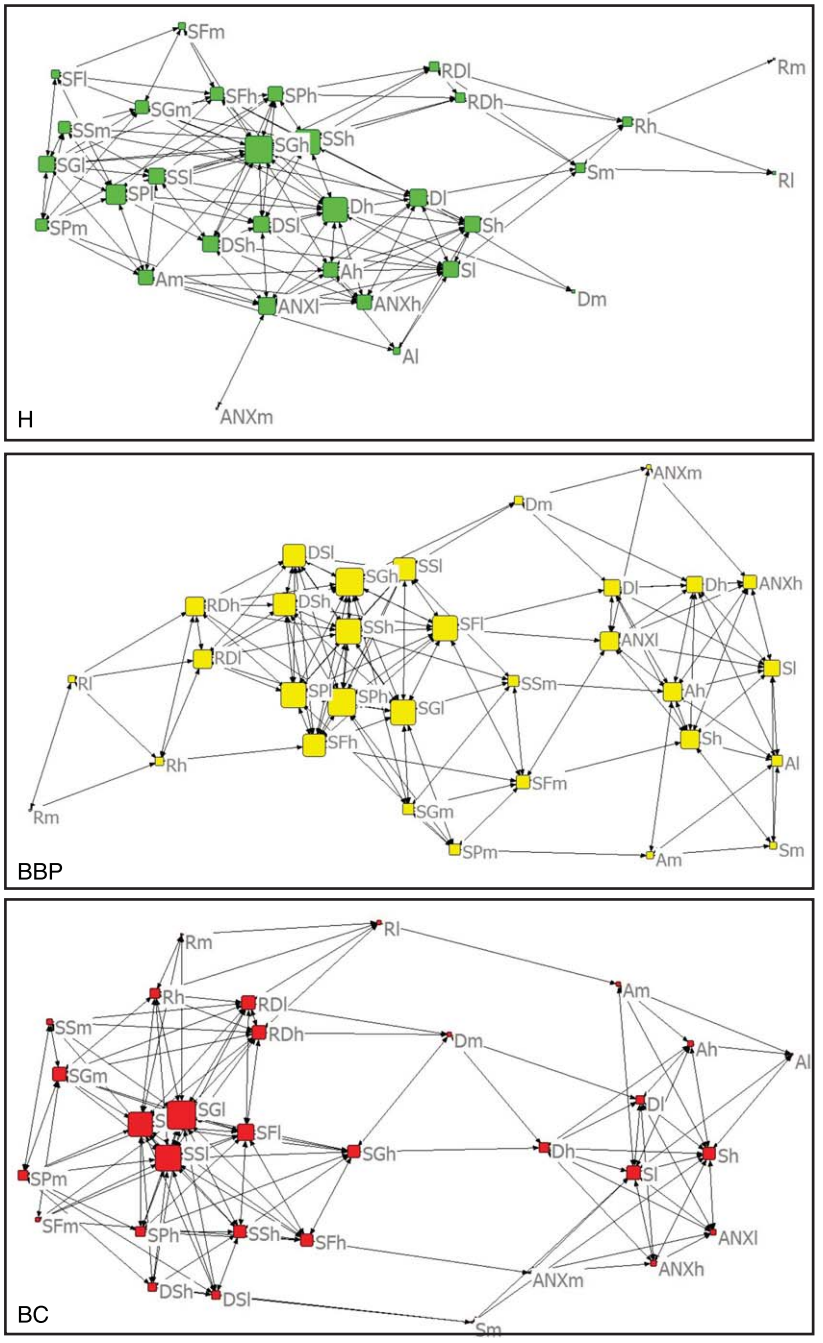

Fig. 1. Spatial and structural organization of psychological networks in healthy (H) women and in women with Benign Breast Pathology (BBP) or breast cancer (BC). Notes: Abbreviations nodes: High Anger Suppression (Ah), Medium Anger Suppression (Am), Low Anger Suppression (Al), High Depression Suppression (Dh), Medium Depression Suppression (Dm), Low Depression Suppression (Dl), High Anxiety Suppression (ANXh), Medium Anxiety Suppression (ANXm), Low Anxiety Suppression (ANXl), High Suppression (Sh), Medium Suppression (Sm), Low Suppression (Sl), High Subjective Experience of Distress (DSh), Medium Subjective Experience of Distress medium (DSm), Low Subjective Experience of Distress (DSl), High Restraint (Rh), Medium Restraint (Rm), Low Restraint (Rl), High Restraint-Defensiveness composition (RDh), Medium Restraint-Defensiveness composition (RDm), Low Restraint-Defensiveness composition (RDl), High Physical symptoms of stress (SFh), Medium Physical symptoms of stress (SFm), Low Physical symptoms of stress (SFl), High Psychological symptoms of stress (SPh), Medium Psychological symptoms of stress (SPm), Low Psychological symptoms of stress (SPl), High Social symptoms of stress (SSh), Medium Social symptoms of stress (SSm), Low Social symptoms of stress (SSl), High Global symptoms of stress (SGh), Medium Global symptoms of stress (SGm) & Low Global symptoms of stress (SGl).

Table 1
Network properties per group

	BC	BBP	H
Number of nodes	31	31	31
Number of links	247	251	254
Diameter	4	1	4
Density	0.267	0.192	0.269
Node with more sociometric degree	SGl	SGh	SGh
Minimum node number	4	2	1
Maximum node number	17	13	17
Node number means	7.97	8.10	8.19
Standard deviation	3.39	3.19	3.78
Variance	11.50	10.16	14.29

Note: *Number of nodes:* maximum number of psychological attributes of women with Breast cancer (BC), with Benign Breast Pathology (BBP) or without breast pathology (H). *Number of links:* maximum number of connections between the nodes of each of the compared groups (BC, BBP or H). *Diameter:* maximum shortest path between two nodes measured by the number of routed links. *Density:* proportion of links in a network relative to the total number of possible links. *Node with more sociometric degree:* number of the node (per group) with more connectivity. *Minimum node number:* minimum number of connected nodes in a network. *Maximum node number:* maximum number of connected nodes in a network.

variance (Table 4). Interestingly, all of the variables guiding the networks' organization in the different groups are psychological. This is particularly certain for variables included in PC2, a component that differed significantly among groups ($P = 0.014$) (Fig. 3). Thus, PC2 clusters the psychological variables that might increase BC susceptibility, a presumption supported by the fact that PC2 variables form a distant, independent cluster in women displaying benign or malign breast pathology (Fig. 1). Thus we confirm the association between the network's distribution and the principal components.

Finally, we conducted a multivariate analysis to further estimate whether suppression of negative emotions could promote BC onset/progression. The model that confronted BC and BBP women suggested, at first, that none of these generic conditions had associations with emotional suppression (Table 5, model 1). However, when H women were compared with BBP or BC patients (Table 5, models 2 and 3), suppression of anxiety was found to be a risk factor to develop breast cancer.

DISCUSSION

Breast cancer is one of the malignant neoplasias that take most women's lives worldwide every year [3]. Timely prediction and early diagnosis are the measures that will surely help us reducing this trend. Clinical researchers have then devised methods

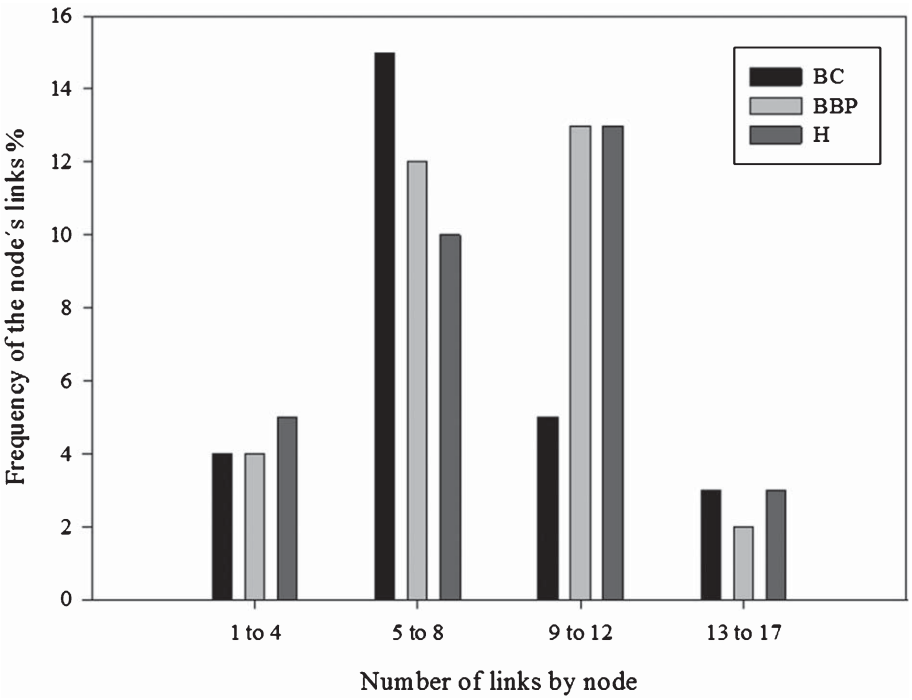

Fig. 2. Frequency of the number of links per node per group. The frequency (%) was grouped in 4 classes according to the number of links in the nodes.

Table 2
Classification of psychological variables according to the number (N) of significant correlations ($P < 0.05$), the average magnitude (M) of the correlations, the connection intensity ($I = N \times M$) and its intensity ranking order (R)

Node	BC				BBP				H			
	N	M	I	R	N	M	I	R	N	M	I	R
SGh	9	0.60	5.44	5	13	0.52	6.81	1	17	0.44	7.50	1
SSh	9	0.59	5.33	6	12	0.49	5.83	6	15	0.46	6.84	2
Dh	8	0.52	4.14	14	8	0.52	4.12	14	15	0.44	6.62	3
Sl	10	0.48	4.78	7	8	0.59	4.69	12	10	0.56	5.57	4
Sh	9	0.53	4.77	8	9	0.56	5.00	9	10	0.51	5.07	5
ANXl	6	0.48	2.88	21	9	0.43	3.88	17	11	0.45	4.99	6
SPl	15	0.51	7.63	3	12	0.50	5.96	4	12	0.41	4.94	7
Dl	7	0.53	3.69	16	8	0.44	3.56	18	11	0.45	4.91	8
SSl	16	0.53	8.48	2	11	0.52	5.71	7	10	0.48	4.83	9
DSh	7	0.47	3.31	19	11	0.45	4.92	10	10	0.46	4.62	10
DSl	6	0.38	2.31	23	11	0.45	4.92	11	10	0.46	4.62	11
SGl	17	0.53	9.06	1	12	0.55	6.57	2	10	0.45	4.46	12
ANXh	6	0.48	2.88	21	7	0.47	3.28	19	9	0.47	4.25	13
SPh	8	0.55	4.41	11	13	0.47	6.16	3	9	0.45	4.03	14
Ah	6	0.50	3.00	20	9	0.48	4.36	13	9	0.44	3.92	15
SFh	9	0.49	4.40	12	11	0.48	5.29	8	8	0.46	3.67	16
SGm	10	0.42	4.17	13	6	0.40	2.42	23	8	0.42	3.35	17
Am	5	0.34	1.71	28	4	0.43	1.74	27	9	0.36	3.26	18
SPm	8	0.44	3.55	17	5	0.39	1.95	25	7	0.43	2.99	19
RDh	10	0.47	4.67	9	9	0.44	3.98	15	6	0.44	2.66	20
RDl	10	0.47	4.67	10	9	0.44	3.98	16	6	0.44	2.66	21
Rh	8	0.47	3.78	15	5	0.50	2.51	22	6	0.43	2.59	22
SSm	6	0.41	2.43	22	6	0.39	2.36	24	7	0.36	2.55	23
Sm	4	0.38	1.51	30	4	0.33	1.33	29	6	0.38	2.28	24
SFl	11	0.54	5.91	4	12	0.49	5.92	5	5	0.45	2.23	25
ANXm	4	0.33	1.32	31	3	0.37	1.12	30	5	0.38	1.90	26
Al	4	0.45	1.79	27	6	0.48	2.90	20	4	0.44	1.74	27
SFm	5	0.37	1.85	25	7	0.38	2.65	21	4	0.38	1.52	28
Rm	4	0.41	1.63	29	4	0.33	1.33	29	1	0.88	0.88	29
Dm	5	0.37	1.84	26	5	0.35	1.77	26	2	0.44	0.88	30
Rl	5	0.46	2.29	24	6	0.39	2.36	24	2	0.36	0.72	31
Totals	247	0.47	3.87		251	0.46	3.81		254	0.45	3.65	

Notes: Highlighted in gray are the most connected nodes ranked from 1 to 10. Abbreviations: High Anger Suppression (Ah), Medium Anger Suppression (Am), Low Anger Suppression (Al), High Depression Suppression (Dh), Medium Depression Suppression (Dm), Low Depression Suppression (Dl), High Anxiety Suppression (ANXh), Medium Anxiety Suppression (ANXm), Low Anxiety Suppression (ANXl), High Suppression (Sh), Medium Suppression (Sm), Low Suppression (Sl), High Subjective Experience of Distress (DSh), Medium Subjective Experience of Distress medium (DSm), Low Subjective Experience of Distress (DSl), High Restraint (Rh), Medium Restraint (Rm), Low Restraint (Rl), High Restraint-Defensiveness composition (RDh), Medium Restraint-Defensiveness composition (RDm), Low Restraint-Defensiveness composition (RDl), High Physical symptoms of stress (SFh), Medium Physical symptoms of stress (SFm), Low Physical symptoms of stress (SFl), High Psychological symptoms of stress (SPh), Medium Psychological symptoms of stress (SPm), Low Psychological symptoms of stress (SPl), High Social symptoms of stress (SSh), Medium Social symptoms of stress (SSm), Low Social symptoms of stress (SSl), High Global symptoms of stress (SGh), Medium Global symptoms of stress (SGm) & Low Global symptoms of stress (SGl).

aimed at predicting the odds of women developing BC along their lifetime [9–11]. However, the predictability of these instruments is about forty percent [12]. There is therefore a need to improve their prediction accuracy. In this regard, we think this goal might be achieved by including the evaluation of psychological variables and the assessment of emotional coping mechanisms, since it has been shown that psychological functions have a great impact on biology and on the health-disease equilibrium, particularly on BC [14–18, 31]. In fact, we have recently proposed a psycho-neuro-immune-endocrine model [31] that hypothetically explains that women with type C personality traits are prone to over-dimensioning environmental challenges, a circumstance that leads to allostatic/pantostatic stress loads [17, 32, 33], supported by the chronic activation of hypothalamic-pituitary-adrenal/gonadal axes (HPA/G) [34]. As a

Table 3
Network disconnections

H vs BC			H vs BBP			BBP vs BC		
Node	Number of disconnections	Disconnected nodes	Node	Number of disconnections	Disconnected nodes	Node	Number of disconnections	Disconnected nodes
Am	7	ANXh, ANXl, SPm, SPl, SSl, SGh, SGl	Dh	8	DSh, DSl, SFh, SPl, SSh, SSl, SGh, SGm	DSh	6	RDh, RDl, SFh, SFl, SPh, SGh
Dh	7	DSh, DSl, SFh, SPl, SSh, SSl SGm	Am	6	ANh, ANl, SPl, SSl, SGh, SGl	DSl	6	RDh, RDl, SFh, SFl, SPh, SGh
Dl	4	Sm, SFh, SSh, SSm	Dl	4	Sh, SFh, SSh, SSm	Ah	3	ANXh, ANXl, SSm
Sm	4	Rh, Rl, RDh, RDl	Sm	4	Rh, Rl, RDh, RDl	RDh	3	SPh, SSh, SGh
Ah	3	ANh, ANl, SGh	ANXl	3	DSh, DSl, SPm	RDl	3	SPh, SSh, SGh
ANXl	3	DSh, DSl, SPm	Sh	3	Rh, SSh, SGh	Am	2	Sm, SPm
Sh	3	Rh, SSh, SGh	ANXh	2	DSh, DSl	Al	2	Dh, Sm
RDh	3	SPh, SSh, SGh	Sl	2	DSh, DSl	Dm	2	ANXm, SSl
RDl	3	SPh SSh, SGh	Ah	1	SGh	ANXl	2	SFm, SFl
ANXh	2	DSh, DSl	SFm	1	SGh	SFm	2	SPm, SSm
Sl	2	DSh, DSl	SPm	1	SSm	Dl	1	SFl
DSh	2	SPh, SGh	SPl	1	SSm	Sh	1	SFm
DSl	2	SPh, SGh	SSh	1	SGm	Rh	1	SFh
SSh	2	SSm, SGm	Al	0		SPh	1	SGm
SFm	1	SGh	Dm	0		SSh	1	SSm
SPh	1	SGm	ANm	0		SGh	1	SGm
SPl	1	SSm	DSh	0		Dh	0	
SGh	1	SGm	DSl	0		ANXh	0	
Al	0		Rh	0		ANXm	0	
Dm	0		Rm	0		Sm	0	
ANXm	0		Rl	0		Sl	0	
Rh	0		RDh	0		Rm	0	
Rm	0		RDl	0		Rl	0	
Rl	0		SFh	0		SFh	0	
SFh	0		SFl	0		SFl	0	
SFl	0		SPh	0		SPm	0	
SPm	0		SSm	0		SPl	0	
SSm	0		SSl	0		SSm	0	
SSl	0		SGh	0		SSl	0	

Notes: The comparisons among groups are displayed in each column (H vs BC, H vs BBP and BBP vs BC). The numbers of missing links in each node are ordered by their magnitude from the highest to the lowest. It is also possible to identify the links missing in each node. Abbreviations: High Anger Suppression (Ah), Medium Anger Suppression (Am), Low Anger Suppression (Al), High Depression Suppression (Dh), Medium Depression Suppression (Dm), Low Depression Suppression (Dl), High Anxiety Suppression (ANXh), Medium Anxiety Suppression (ANXm), Low Anxiety Suppression (ANXl), High Suppression (Sh), Medium Suppression (Sm), Low Suppression (Sl), High Subjective Experience of Distress (DSh), Medium Subjective Experience of Distress medium (DSm), Low Subjective Experience of Distress (DSl), High Restraint (Rh), Medium Restraint (Rm), Low Restraint (Rl), High Restraint-Defensiveness composition (RDh), Medium Restraint-Defensiveness composition (RDm), Low Restraint-Defensiveness composition (RDl), High Physical symptoms of stress (SFh), Medium Physical symptoms of stress (SFm), Low Physical symptoms of stress (SFl), High Psychological symptoms of stress (SPh), Medium Psychological symptoms of stress (SPm), Low Psychological symptoms of stress (SPl), High Social symptoms of stress (SSh), Medium Social symptoms of stress (SSm), Low Social symptoms of stress (SSl), High Global symptoms of stress (SGh), Medium Global symptoms of stress (SGm) & Low Global symptoms of stress (SGl).

Table 4
Saturation factor of principal components (PC1 and PC2) from the linear combination of the psychological and clinical variables

Variable	PC1	PC2
Age	0.08	–0.22
BC heritage	–0.29	0.05
Overweight	0.21	–0.11
Obesity	–0.10	0.09
Tobacco smoke	–0.04	–0.04
Alcoholism	–0.12	0.14
Other addictions	–0.18	0.12
Early menarche	–0.26	–0.07
Late menopause	–0.08	0.00
Pregnancy	–0.22	0.36
Labor	0.21	–0.30
Abortion	0.04	–0.15
Caesarean section	0.01	0.14
Age at first birth	–0.04	0.02
Hormonal contraceptives	0.11	0.18
Lactation	–0.25	0.41
Hormone replacement therapy	0.09	–0.13
High Anger Suppression (Ah)	0.04	–0.67
Medium Anger Suppression (Am)	0.12	0.11
Low Anger Suppression (Al)	–0.15	0.56
High Depression Suppression (Dh)	–0.21	**–0.77**
Medium Depression Suppression (Dm)	0.27	0.16
Low Depression Suppression (Dl)	–0.04	0.65
High Anxiety Suppression (ANXh)	–0.01	–0.60
Medium Anxiety Suppression (ANXm)	0.01	0.00
Low Anxiety Suppression (ANXl)	–0.01	0.60
High Suppression (Sh)	–0.10	**–0.82**
Medium Suppression (Sm)	0.10	–0.06
Low Suppression (Sl)	0.01	**0.83**
High Subjective Experience of Distress (DSh)	–0.50	–0.26
Low Subjective Experience of Distress (DSl)	0.50	0.26
High Restraint (Rh)	0.36	–0.10
Medium Restraint (Rm)	–0.20	0.10
Low Restrain (Rl)	–0.19	0.00
High Restraint-Defensiveness composition (RDh)	0.47	0.06
Low Restrain-Defensiveness composition (RDl)	–0.47	–0.06
High Physical symptoms of stress (SFh)	–0.66	–0.06
Medium Physical symptoms of stress (SFm)	–0.18	0.26
Low Physical symptoms of stress (SFl)	**0.77**	–0.17
High Psychological symptoms of stress (SPh)	**–0.71**	–0.09
Medium Psychological symptoms of stress (SPm)	–0.21	0.15
Low Psychological symptoms of stress (SPl)	**0.81**	–0.07
High Social symptoms of stress (SSh)	**–0.76**	–0.17
Medium Social symptoms of stress (SSm)	–0.19	0.24
Low Social symptoms of stress (SSl)	**0.84**	–0.01
High Global symptoms of stress (SGh)	**–0.81**	–0.14
Medium Global symptoms of stress (SGm)	–0.13	0.30
Low Global symptoms of stress (SGl)	**0.88**	–0.11
Expl.Var	6.82	4.99
Prp.Totl	0.14	0.10

Notes: In addition, we show the score and percentage of variance explained in the multivariate analysis.

result, increased levels of estrogens secreted by the ovaries and by body fat could elevate the risk of developing BC [34]. Chronic stress loads could raise prolactin serum concentrations leading

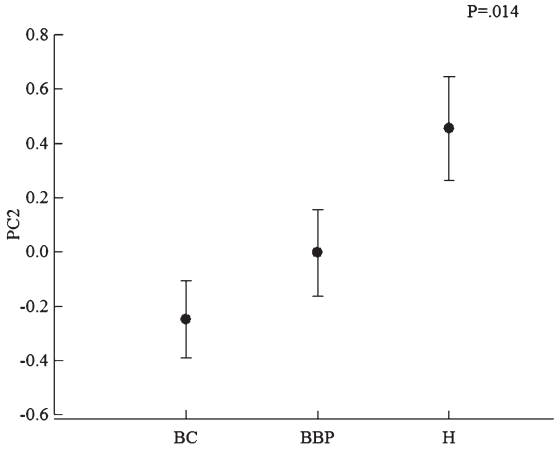

Fig. 3. Mean values (±CI 95%) of the factor score for the linear combination of PC2 vs H, BBP & BC. Mean values also describe the Generalized Linear Model adjustment and the percentage of variance explained (r^2).

to decreased immune surveillance [32, 35–40], particularly chronic stress suppresses natural killer and T cell responses [28], mononuclear cell counts [29] and increases serum levels of the pro-inflammatory interleukins IL-6 and IL-8 [30]. In addition, as it was mentioned previously, three possible scenarios may biologically contextualize the existing links between emotions and disease: 1) maladaptive reactions may induce excessive physiological activation [22, 23]; 2) chronic maladaptive emotions could develop and consolidate noxious habits; and 3) negative emotions could also favor disease states [24].

In a previous work [41], we showed that low emotional restraint, low global stress symptomatology, low physical stress symptoms, low restraint-defensiveness composite and high distress, are personality variables and emotional coping styles that might increase the odds of Mexican women to develop BC. Even these results show new avenues for a more complex, integrative and earlier BC diagnosis method, there are several questions, in particular, those concerning the greater suppression of anxiety and not anger in Mexican women; and the lower levels of stress symptoms founded in BC women. Therefore, it would be interesting to study the relationship between the psychological variables and their interaction with the clinical ones. In this complementary manuscript, we showed that psychological variables that estimate emotional containment and psychobiological stress have a more disconnected network distribution in women that were diagnosed with BC followed by BBP patients, as compared

Table 5
Multivariate model of anger, depression and anxiety suppression (dependent variable: breast cancer)

Variables	Crude model			Adjusted model		
Model 1: women with breast cancer vs women with or without benign disease pathology						
	OR	CI 95%	*p*	OR	CI 95%	*p*
Anger suppression	1.09	(0.99–1.19)	0.09	1.09	(1.01–1.18)	0.32
Depression suppression	0.95	(0.86–1.05)	0.33	–	–	
Anxiety suppression	1.08	(0.97–1.20)	0.14	–	–	
Model 2: women with breast cancer vs women with benign disease						
	OR	CI 95%	*p*	OR	CI 95%	*p*
Anger suppression	1.09	(0.98–1.22)	0.10	–	–	
Depression suppression	0.95	(0.84–1.07)	0.36	–	–	
Anxiety suppression	1.03	(0.91–1.16)	0.65	–	–	
Model 3: women with breast cancer vs women without pathology						
	OR	CI 95%	*p*	OR	CI 95%	*p*
Anger suppression	1.07	(0.96–1.19)	0.24	–	–	
Depression suppression	0.94	(0.83–1.07)	0.36	–	–	
Anxiety suppression	1.16	(1.01–1.33)	0.04	1.15	(1.03–1.27)	<0.01

Notes: OR = Odds ratio; CI = Confidence interval. ORs calculated by logistic regression. Those variables adjusting the ORs are not shown.

with H women. These results on the light of the psycho-neuro-immune-endocrine model previously proposed [31] confirm that the deregulation of the stress response by the emotional suppression predisposes the onset and development of BC. Thus, our network analyses revealed that psychological variables had a greater relative weight when driving the structure and spatial organization of the network and therefore when identifying women with higher proclivity to develop BC than family, reproductive, nutritional and life style factors. It is then likely that including psychological assessments might improve our chances of identifying BC-susceptible women during regular medical checkups. Clearly, prospective longitudinal studies are needed to evaluate the merits of this suggestion.

In addition, the network analysis performed in the present study allowed us to pin point specific psychological variables that might predispose women to develop BBP and BC. In particular, anger and anxiety suppression were the most prominent hubs in women that were later diagnosed with BC. This fact could be explained through neurobiological observations. It has been shown that anger and anxiety suppression alter the fear/anger response of the amygdala. This may decrease the response of the ventral prefrontal cortex and its connectivity with the hippocampus [66]. Thus, these neurobiological changes could predispose women of being incapable of freeing their emotions after first appraisal of the challenge, and also incapable of confronting it successfully; and then, they turn to use negative coping skills to "deal" with the challenge. This circumstance throws her bodies into an exacerbated chronic stress response in which the modulatory negative feedback is dysfunctional. These events will tend to promote inflammation initially but, in the long run, will suppress NK cell mediated innate and T and B cell mediated adaptive immune responses and, with this, will eventually promote the emergence of BC [31].

However, the identification of specific personality traits or coping mechanisms that might predispose women to develop BBP and/or BC, is not the only aspect that may be used to estimate each women's propensity to develop benign or malign breast pathologies. The overall organization of the psychological network, the relative interconnectedness among nodes and hubs of the psychological variables and the spatial arrangement of the network (e.g., variable clustering) may be used as blueprints of H women and women with BBP and BC. Indeed, although network connectivity (number of nodes, links, and intensity of connections) did not show statistically significant differences among H, BBP and BC groups, they do when their spatial network distribution was compared. That is, while H women displayed a coherent and connected topology, the BBP and BC patient networks were progressively disconnected and gave rise to two clusters that became more distant as the disease worsened. This is consistent with predictions of the network theory that sustains that 1) the organisms having networks with greater number of highly connected hubs will be more resilient [56, 67] (women with BC had fewer highly connected hubs than H women and women with BBP) and 2) that the organisms that shift the most the configuration of their network are more prone to develop diseased functional states [67, 68]. Under this

scenario, BBP seems to be a transitional state, a prediction consistent with the medical presumption that BBP may predispose to BC [69].

Previous studies have shown that the lack of stress perception, as monitored through reports on global stress symptoms and the subjective experience of distress, leads to emotional suppression [70]. In our study, BC patients do not express negative emotions as a need to gain harmony but rather repress their feelings and needs in order to meet other people's needs [5, 42]. This might explain why Global symptoms of stress (SG) is the preeminent hub in BC patient's network and why the most disconnected node is the one representing the high subjective experience of distress (DSh). Thus, women propensity to develop BC might be unable to perceive both the distress symptoms and the subjective aspect of stress; furthermore, this lack of stress perception is related to emotional suppression [71]. Principal component analysis supports this conclusion. Indeed, while the network of H women displayed the psychological variables associated with distress and with the emotional suppression in the main cluster, the networks of BBP and BC patient showed both variables in two clusters.

Studies by Barabasi et al. (2011) [68] suggest that when networks representing diseased states display modular arrangements, there is always a module that contains the variables that explains the development of disease. If we assume this assertion as probable, the results obtained through the principal component analysis, supports the fact that the relative weight of nodes (representing suppression of depression, anger, anxiety and global suppression) clustered in PC2 might be much greater than that of stress-related nodes (SFl,SPh, SPl, SSh, SSl, SGh, SGl) clustered in PC1, when identifying women under the risk of developing breast pathology. Our prediction is compatible with the Lazarus' theory (2000) [72] that states that stress responses are instrumented after engaging them following the expression of negative emotions and the modification of life styles (also see Piqueras, Ramos, Martinez, & Oblitas (2009) [22].

A fundamental result obtained in our research is that none of the non-psychological factors currently accepted to predispose individuals to BC (i.e., genetic, hormonal or lifestyle; [3–7]) contributed significantly to the variance in our sample of 150 Mexican women, as shown by the PC analysis. In contrast, emotional suppression (PC2) did (Table 4, Fig. 3). These results suggest that, at least for our small sample of Mexican women, psychological traits might predict better the odds of a woman develop BC. Hence, introducing psychological profiling into current methods used to identify women susceptible of develop BC may improve their percent predictability.

Hence, in BC and BBP patients, emotional suppression might predispose women to develop breast pathologies (Model 2: Table 5). However, when BBP and BC patients are compared against H women, anger and anxiety suppression rise up as key predicting risk factors of breast pathology. It is interesting that in the case of the BC and H comparison the key psychological feature was the suppression of anxiety. This is in accordance with previous results showing that Mexican women diagnosed with BC suppress more anxiety than anger [41].

In sum, we showed that the assessment of emotional containment and psychobiological stress through network and PC analyses may increase our chances of identifying women susceptible of developing BC, at least among Mexican women. We recognized, nonetheless, that our cross-sectional study in a one-time survey with 150 women has a restricted representativeness. We also acknowledge that, given the type C personality is not exclusive for cancer propensity but also for chronic diseases in general [18, 73]. Hence, prospective longitudinal studies are clearly needed to replicate and strengthen the merits of our ideas.

AUTHORS' CONTRIBUTIONS

IMN participated in the design of the study and in statistical analysis. YCU participated in statistical analysis. TRG and CL participated in the study design, the statistical analysis and its coordination. TRG and IMN drafted the manuscript together. GGO and MRHP conducted a critical review of the manuscript. All authors read and approved the final manuscript.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol was reviewed and approved by the Ethical Committee for Clinical Research at the Hospital General de México "Dr. Eduardo Liceaga", Secretaría de Salud (DI/12/111/03/064). GGO academic exchanges were financially supported by the Coordinación de la Investigación Científica, Universidad Nacional Autónoma de México and by the Dirección General de Relaciones Internacionales Coordinación de Movilidad Estudiantil y Académica, Universidad Veracruzana.

CONFLICT OF INTEREST

All authors declare that there are no conflicts of interest.

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