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Original Research Article

Searching for the emotional roots of breast cancer: A cross-disciplinary analysis integrating psychology, Chinese medicine, and oncology biomarkers

Ofer Baranovitch [a,b,*], Meirav Wolff-Bar [c,d], Meora Feinmesser [c,d], Chen Sade-Zaltz [c,d], Ilan Tsarfaty [e], Victoria Neiman [d,f]

[a] Integrative Unit, Davidoff Cancer Center, Rabin Medical Center, Petach Tikva 4941492, Israel
[b] Maccabi Tivi (Maccabi Health Organization), Tel Aviv 6801294, Israel
[c] Department of Pathology, Rabin Medical Center, Petach Tikva 4941492, Israel
[d] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 6997801, Israel
[e] Department of Clinical Microbiology and Immunology, Sackler School of Medicine, Tel Aviv University, Tel Aviv 6997801, Israel
[f] Institute of Oncology, Davidoff Cancer Center, Rabin Medical Center, Petach Tikva 4941492, Israel

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ABSTRACT

Objective: We employed a multidisciplinary approach incorporating theoretical ideas, clinical experience, psychology, physiology, traditional Chinese medicine (CM), modern practice of CM, and oncology to explore the effect of patients' repression of negative emotions and traumatic events on breast cancer (BC) pathogenesis.
Methods: BC female patients, older than 18 years of age, with available pathology reports who were treated at Rabin Medical Center were recruited. All participants completed questionnaires regarding medical history, behavioral tendencies, negative emotions, trauma, symptoms, and pathology (from a CM perspective). Data on tumor characteristics were collected from the pathology reports. The associations were examined using hierarchical binary logistic regressions.
Results: A total of 155 BC patients were enrolled. The median age was 52 years, with a range of 26–79; 95% were mothers; 28% had estrogen receptor (ER)-negative BC, 52% had progesterone receptor (PR)-negative BC, 48% had human epidermal growth factor receptor 2-negative BC, and antigen Ki-67 $\geq$ 20% was reported for 52% of tumors. Statistically significant associations were found between the emotional markers (sense of motherhood failure, and lack of self-fulfillment), avoidance behavior, and physical symptoms that are related to emotional repression based on CM. Significant associations were also found between variables associated with physical symptoms of emotional repression, which involves the production and accumulation of non-substantial phlegm (i.e., "high-lipid Qi-like microscopic phlegm"), avoidance behavior which unconsciously uses "high-lipid Qi-like microscopic phlegm" in order to achieve emotional repression, and tumor parameters including tumor grade, PR status, and Ki-67. Patients with higher levels of "high-lipid Qi-like microscopic phlegm" were more likely to have tumors with worse prognosis (PR-negative, higher grade, and higher Ki-67).
Conclusion: We demonstrated a relationship between emotional parameters, behavioral tendencies, CM parameters, and oncologic parameters in BC. Additional research is warranted to explore these associations and their relevance to clinical practice.

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1. Introduction

Breast cancer (BC) is the second most common cancer, behind only skin cancer, and the leading cause of cancer-related deaths

* Corresponding author at: Integrative Unit, Davidoff Cancer Center, Rabin Medical Center, Petach Tikva 4941492, Israel. Tel.: +972545884789.
E-mail addresses: ofer_b@mac.org.il, oferbaranovitch@gmail.com (O. Baranovitch).

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among women [1]. Evidence suggests that stress may be involved in BC development, through a mechanism involving the stress hormone cortisol [2,3]. However, cortisol is only a component of the mind-body relationship in the context of tumor pathogenesis; additional markers are required to broaden our understanding of the relationship between the emotional world and BC pathogenesis. Notably, the role of negative emotions and their repression in BC etiology is yet to be elucidated [4].

In this study, we employed a multidisciplinary approach that incorporated clinical experience, theory, psychology, physiology, traditional and modern Chinese medicine (CM), and oncology to describe a novel model of the mind-body relationship, and used it to explore the effects of repressed negative emotions and trauma on human BC pathogenesis.

CM is the main modality used in our model (see Table S1 for CM definitions). CM views each organ system as representing a complete set of materialistic and non-materialistic phenomena. Each organ system includes the organ itself, as we refer to it in modern medicine, and its Qi, unique Shen part and emotions. All organ systems are connected to form one holistic entity, via a meridian network, which includes deep and superficial pathways. CM views the liver Qi as the Qi and emotional regulator of all organs. Therefore, liver Qi stagnation or constraint represents emotional imbalance and depressed emotions [5].

Phlegm is a key component in CM theory for physical, mental, and emotional pathologies. It is a water-based gel, consisting of glycoproteins, immunoglobulins, lipids, and other substances. The phlegm is produced by the lungs, stomach, intestines and other mucosal tissues to protect against foreign penetration, toxicity, and irritation. CM uses the term "phlegm-damp" to describe metabolic disorders such as obesity. Under healthy circumstances, fatty tissues normally surround body parts in order to preserve heat and provide protection from the environment. But pathological "phlegm-damp" occurs when excessive accumulation oversaturates the fatty tissues. Pathological excessive phlegm and a phlegm-damp body environment can occur as a result of overconsumption of damp and fatty foods, which alter the viscosity of the entire body's fluids [6]. Prolonged and intense emotional upset causes Qi stagnation, which eventually can produce internal heat. Over time, the combination of excess heat plus phlegm-damp in the internal environment causes the phlegm-damp to gradually lose its moisture and turn into phlegm-heat [7]. Phlegm gradually loses its substantial-watery form and turns into non-substantial phlegm, which is described hereafter as "high-lipid Qi-like microscopic phlegm." Such phlegm is known to exacerbate mental and emotional pathologies. Phlegm can penetrate any anatomical, functional, or energetic space as well as the meridian pathways, thereby altering all physiological communication routes. Phlegm is obstructive and affects all circulatory systems in the body depending on its water-lipid ratio, and the space being affected. The physiological equivalent of phlegm is unclear, although evidence suggests that it can alter cellular membrane biochemistry [8,9], and the prevalence of coronary heart disease, ischemic stroke, and hypertension is significantly higher among patients with phlegm syndromes as classified in CM [10,11]. Moreover, patients diagnosed with phlegm syndromes present plasma constituent concentrations of fatty acid groups, unsaturated lipids, and low-density lipoprotein which are significantly higher than non-phlegmatic patients [12]. We hypothesize that "high-lipid Qi-like microscopic phlegm" alters electro-magnetic fields of critical structures leading to physiological and molecular changes (e.g., errors in cell signaling and changes in DNA methylation profiles) that could result in cancer development [13,14]. We further hypothesize that patients' unconscious efforts to discharge such phlegm requires an alteration in its water-lipid ratio. Therefore, the proportion of water in the "high-lipid Qi-like microscopic phlegm" needs to increase so the thicker phlegm-heat can return to the more fluid phlegm-damp state and eventually be discharged from the body.

Our cross-disciplinary model suggests a link between CM mind-body theory, CM modern research, and psychology; and specifically, psychological defense mechanisms. We hypothesize that phlegm, in different viscosity, is produced by one's own mind-body unconscious intelligence when such mechanisms are activated. The "foggy" nature of phlegm enables repression of overwhelming core-sensations, negative emotions, and traumatic imprints which allows maintenance of normal life activities and well-being [15]. This fogginess is achieved by alterations of biological and physiological communication routes. We further hypothesize that phlegm is produced to buffer emotions that are threatening or harmful, such as those associated with a problematic relationship with a dominant figure in one's life. The potential penetrative nature of pathogenic Qi into the meridians and the use of phlegm as a defensive mechanism can be understood as reflected in the syndrome "phlegm blocking the meridians [7]." We also hypothesize that liver Qi stagnation is directly proportional to one's intelligence, and is mixed with phlegm at the depth of the unconscious realms, creating a "mask" ("high-lipid Qi-like microscopic phlegm") which blocks negative emotions and traumatic imprint from surfacing into the consciousness [5].

Another relevant CM concept is the conception vessel (CV) and governing vessel (GV), two meridians that form one continuous pathway along the anterior and posterior midline of the body. The CV Qi dominates femininity and as such is involved in breast pathologies and estrogen regulation, whereas GV Qi dominates masculinity and progesterone [16,17]. The penetrating vessel (PV) governs all blood circulation in the body and involves Qi distributions to all Qi pathways. In females, it governs menstruation, fertility, and breastfeeding. All traumatic imprints are memorized within the PV's blood network. "High-lipid Qi-like microscopic phlegm" deposition metaphorically wraps the part of Shen which resides within the blood, thereby promoting emotional repression and preventing release of emotions on the conscious level [7,18]. With time, repression results in the formation of "blood-stasis phlegm" pathologies such as coronary heart disease, ischemic stroke, hypertension, and cancer [10,11].

The concept of barriers is found in physiology (e.g., the blood brain barrier), psychology (psychological barriers are defined as envelopes that wrap concealed emotions in different levels of consciousness [19]), and CM, which defines the mind and the body within a set of envelopes, separated by barriers, that constantly communicate while regulating emotional repression and release [18]. Altering the communication (e.g., by "high-lipid Qi-like microscopic phlegm" deposition) may contribute to various pathologies, including cancer. The CM meridian theory may provide a link between the "non-material" concept of defensive psychological barriers and the "material" physiological and anatomical ones. The Dai extraordinary meridian and the diaphragm muscle are barriers. They share a similar physical placement in the body, as both divide lower from upper body zones. As barriers, they are in charge of Qi, Shen, and emotional sorting and regulation. CM views unconscious repression of negative emotions and trauma as being achieved by compressing them downward (underneath the diaphragms' barrier) and holding them in (through the cell membrane) [18]. The ability to counteract the resurfacing of repressed emotion depends on "high-lipid Qi-like microscopic phlegm" build-up within the Dai, diaphragm, and cellular-membranes.

In CM, the cellular membrane is considered a microscopic form of the Dai meridian [15]. We hypothesize that "high-lipid Qi-like microscopic phlegm" deposition within the cell membrane alters cell membrane biochemistry and its electromagnetic balance,

thereby affecting cellular signaling. This hypothesis is supported by findings from CM studies examining cancer patients who were diagnosed with "phlegm-stasis" syndrome, and their plasma showed elevated fat metabolism and decreased levels of various amino acids, resulting in changes in the cell membrane [8,9], which could impact signal transduction and lead to cancer proliferation, and potentially to reduced immunity of the host to the cancer [20]. Furthermore, retention of "high-lipid Qi-like microscopic phlegm" within the blood, as a by-product of trauma repression, alters permeability of blood vessels and affects angiogenesis, which could also impact cancer development [21].

In the current study, we investigated the effect of three emotion-related markers: failure to live up to one's own expectations of motherhood, lack of self-fulfillment, as well as sudden death of or separation from a loved one and its traumatic imprint on BC. In CM, these emotions are perceived as affecting the CV, the primary meridian involved in BC, and repression of traumatic episodes is perceived as impacting the PV, which is also involved in BC. The association of these markers, as determined via questionnaires, CM markers for repression of negative emotions or trauma, and oncology biomarkers (tumor grade, levels of the proliferation factor antigen Ki-67, hormone receptor status based on estrogen receptor [ER] and progesterone receptor [PR] status, and human epidermal growth factor receptor 2 [HER2] status) was investigated.

The emotional markers (EMs) were chosen as such because we hypothesized that BC onset or pathogenesis is, in part, a reflection of the patients' self-perception of their own motherhood performance. We hypothesized that the state of the CV (Qi pathway and Qi field) reflects one's accumulated experiences of motherhood functionality and emotional states throughout life. Psychological repression is achieved by compressing this sense, and the negative emotions that are consequently evoked by it, into the depth of the CV and its infinite extensions in every cell, leading to a physiological repression targeting the cell membranes and nuclei of the mammary glands and ducts that are being governed by CV Qi. Another EM chosen for this study is lack of self-fulfillment, as self-fulfillment has a central role in maintaining spiritual and emotional well-being [22]. CM recognizes that unease of the Hun (a spiritual entity), which resides within the liver organ and Qi field, and plays an important role in reaching one's destiny and unique life path, may lead to liver Qi stagnation and emotional imbalance [15,23]. In CM, lack of self-fulfillment is often accompanied by multiple physical symptoms including chronic fatigue symptom, neck symptoms, thyroid problems, and more. Lack of self-fulfillment and the negative emotions associated with it are often unconsciously repressed. Notably, there may be correlations between a sense of failed motherhood and lack of self-fulfillment, as realizing one's motherhood obligations is often idealized as a significant source of fulfillment. Another EM chosen for the current analysis is sudden death of or separation from a loved one, as such an event clearly leads to physical, cognitive, and emotional distress [24]. In CM, a sudden traumatic event is considered an external pathogenic cold that penetrates deeply, affecting Shen, and the PV blood and Qi circulation, thereby causing blood-stasis [25]. Surviving trauma requires construction of psychological defensive barriers, leading to extensive unconscious production of "high-lipid Qi-like microscopic phlegm" and its deposition within such barriers. The mechanisms associated with emotion suppression and sudden trauma differ, as in the former, the process is gradual and the person is more aware of it; whereas, in a traumatic situation, repression is an automatic reflex that affects the PV blood circulation, and remains in the memory of the PV's blood, affecting "material" and "non-material" realms of life. We hypothesized that "high-lipid Qi-like microscopic phlegm," which participates in the repression of traumatic events, and its deposition within the blood, can gradually become pathological, leading to the development of "phlegm and blood-stasis syndrome" diseases [12]. We further hypothesized that the traumatic loss of a close feminine or masculine figure is memorized within the CV or GV pathways and Qi fields, respectively, for good.

Repression markers (RMs) represent different ways to identify repression of negative emotions. Such repression involves phlegm and Qi production and deposition. For example, a patient may suffer from phlegm-damp discharge symptoms or pathologies (CM), which suggests an unconscious need to reduce "high-lipid Qi-like microscopic phlegm" accumulation within barriers (RM1). Another example is a patient's pain as a marker for intensity of repression of negative emotions and trauma (RM2). We clinically validated the correlation of lower body pain (under the Dai vessel or diaphragm barrier) and repression of negative emotions [18]. The pains reflect repression on the longitudinal plane of the body, and they also reflect repression on the perpendicular plane, deep through the cell membrane into the cell nucleus. The intensity of the pain can measure the Dai-barrier's efforts to counteract the natural tendency of repressed emotions to surface outward to the superficial levels of consciousness on both planes. A patient's repression pains along the CV and GV pathways and below the Dai-barrier are markers for phlegm deposition intensity. The above two "physical" markers (RMs 1 and 2) are means to assess a patient's emotional terrain without her being aware of that, thus optimizing data collection and reducing bias. RM3 measures the intensity of a patient's avoidance behavior in confronting difficult issues such as negative emotions and conflicts, and RM4 measures the tendency of the patient to avoid open verbal communication with someone who is a difficult but important figure in the patient's life. Therefore, in this case, "high-lipid Qi-like microscopic phlegm" is being deposited in two planes: outward, between the patient and the figure; and inward, enmeshed within the patient' own consciousness levels.

2. Methods

The study was approved by the Rabin Medical Center (RMC) review board (RMC 16-0237). Informed written consent was obtained from each subject. This study took place at the Davidoff Cancer Center, RMC, from May 2016 until September 2018.

2.1. Participants

BC female patients treated in RMC (as an outpatient undergoing standard cancer treatment or in the integrative oncology unit at RMC) were recruited to the study. All BC patients > 18 years of age with available pathology reports were eligible. There were no restrictions with respect to disease status (ongoing *vs.* in remission).

2.2. Study design

This was an observational cross-sectional study. After obtaining informed consent, data were collected from each patient at a single timepoint (patients were not followed further). Table 1 summarizes the study parameters. There were three types of variables: EMs (EM1–4), RMs (RM1–4), and biological markers including tumor grade, Ki-67, ER, PR, and HER2. The EMs and the RMs were determined from the responses of the patients to questionnaires regarding medical history, behavioral tendencies, negative emo-

Table 1
Summary of markers used in the current analysis.

Marker class	Marker name	Marker description	CM relevance	Conventional medicine relevance	Psychology relevance	Questions used to calculate the marker result (see Table S2)	Potential outcomes
EMs: markers of negative-emotion intensity, and the occurrence of traumatic event	EM1	A sense of motherhood failure (core sense)	CV meridian pathway and Qi field, breasts	NA	Negative emotion	12 questions with 1–5 scoring. Score $\geq$ 4 was considered "Yes"	No: 0 "Yes" response Yes: $\geq$ 1 "Yes" response
	EM2	Lacking self-fulfillment sensation—behavioral/emotional (core sense)	Hun, Shen, Tao, liver Qi	NA	Negative emotion	4 questions with 1–5 scoring. Score $\geq$ 4 was considered "Yes"	No: 0 "Yes" response Low: 1–2 "Yes" responses High: 3–4 "Yes" responses
	EM3	Lacking self-fulfillment sensation—physical (core sense)	Liver and gall-bladder Qi, Shao-yang stage	NA	Negative emotion, psycho-somatic symptoms	4 questions with yes/no answers	No: 0 "Yes" response Low: 1–2 "Yes" responses High: 3–4 "Yes" responses
	EM4	Sudden loss and/or sudden separation of/from a loved and close figure (trauma)	Blood-stasis, cold damage, PV blood-vessel network, breasts, CV or GV	NA	Trauma	4 questions with yes/no answers	No: 0 "Yes" response Yes: $\geq$ 1 "Yes" response
RMs: phlegm-spectrum depositions within barriers and their discharge	RM1	Phlegm-damp symptom and pathology intensity	Discharge any barrier's phlegm, phlegm-damp pathologies	NA	Psycho-somatic symptoms	21 questions with yes/no answers	No: 0 "Yes" response Low: 1–2 "Yes" responses Medium: 3 "Yes" responses High: $\geq$ 4 "Yes" responses
	RM2	Physical symptom intensity	GV, CV, and Dai meridian pathways	Associated with PR and ER regulation, cell membranes, cellular signaling, and DNA methylation	Psycho-somatic symptoms	4 questions with yes/no answers	No: 0 "Yes" response Low: 1–2 "Yes" responses High: 3–4 "Yes" responses
	RM3	Behavioral tendency to avoid negative emotions, and deposition of "high-lipid Qi-like microscopic phlegm"	GV, CV, and Dai meridian pathways	Associated with PR and ER hormonal regulation, cell membranes, cellular signaling, and DNA methylation	Associated with patients' own consciousness levels	4 questions with 1–5 scoring. Score $\geq$ 3 was considered "Yes"	No: 0 "Yes" response Yes: $\geq$ 1 "Yes" response
	RM4	Behavioral tendency to avoid difficult relationships, and deposition of "high-lipid Qi-like microscopic phlegm"	GV, CV, and Dai meridian pathways	Associated with PR and ER regulation, cell membranes, cellular signaling, and DNA methylation	Associated with patients' own consciousness levels and with relationship with close figure	2 questions with 1–5 scoring. Score $\geq$ 3 was considered "Yes"	No: 0 "Yes" response Yes: $\geq$ 1 "Yes" response
Tumor biologic markers	Grade	Tumor grade: low [grade 1], intermediate [grade 2], and high [grade 3]	NA	A prognostic factor (higher grade, worse prognosis)	NA	NA	Grades 1, 2 or 3
	Ki-67	Proliferation marker	NA	A prognostic factor (higher proportion of cells expressing Ki-67, worse prognosis)	NA	NA	Low: < 12% Medium: $\geq$ 12%, < 20% High: $\geq$ 20%
	ER	ER status	NA	Used to predict response to endocrine therapy	NA	NA	Negative to high (0–3)
	PR	PR status	NA	Used to predict response to endocrine therapy	NA	NA	Negative to high (0–3)
	HER2	HER2 status	NA	Used for prognosis and predicting response to anti-HER2 therapy	NA	NA	Negative to high (0–3)

CM: Chinese medicine; CV: conception vessel; EM: emotional marker; ER: estrogen receptor; GV: governing vessel; HER2: human epidermal growth factor receptor 2; PV: penetrating vessel; NA: not available/not applicable; PR: progesterone receptor; RM: Repression marker.

tions and trauma in conscious memory, and symptoms and pathology from a CM perspective (see Table S2 for the questionnaire itself). Biological markers were extracted from the pathological reports.

Some parts of the questionnaire (i.e., EM3, EM4, RM1, and RM2) consisted of questions with a yes/no answer. For the markers which were comprised of multiple yes/no questions, the symptoms were considered more severe with submission of more "yes" responses (Table 1). Other markers (i.e., EM1, EM2, RM3, and RM4) used a 1–5 scale (not relevant [1] to severe [5]). For these markers, score of ≥ 3 or ≥ 4 was considered a "yes" and the number of "yes" responses for the marker determined the outcome (No/Yes or No/Low/High; see Table 1). A member of the research team was present for assistance when patients completed the questionnaires; however, they were blinded to the patient's pathology. Data on histology, grade, ER, PR, Ki-67, and HER2 were collected from the pathology reports. These biological markers were chosen as they are related to the molecular mechanisms associated with BC development and proliferation, and as they are routinely assessed in BC to determine prognosis and guide treatment decisions.

2.3. Statistical considerations

The parameters included in the study are summarized in Table 1. Descriptive statistics were used to summarize the findings. A Cronbach's α reliability test was performed in order to measure internal consistency of the questionnaires. A principal component analysis (PCA) with a forced 4-component extraction and Varimax rotation method was run on all the scaled questions, in order to reduce those questions into 4 smaller components and compare this grouping to the one used in the paper. Hierarchical binary logistic regressions were used to examine the associations between the study parameters. All statistical analyses were performed with Statistical Packages of Social Sciences Software (SPSS), Version 23.0 (IBM Corp. 2015), and IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY. IBM Corp.). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Study population

The analysis included 155 female BC patients. The vast majority of patients had infiltrating ductal carcinoma (92%); the median age was 52 (range: 26–79) years, and 95% were Israeli Jewish. Approximately a quarter (28%) had ER-negative disease and approximately half (48%) were HER2-negative (Table 2). Almost all patients (95%) were mothers. Of the 155 patients, 116 (75%) indicated that they had a hard-to-cope with figure in their lives, whereas the rest indicated that they had no such figure. Patients with BC characteristics associated with more aggressive disease tended to be younger. Patients with ER-negative BC had a median age of 47.5 (range: 27–73) years, *vs.* 52.9 (range: 26–79) years for those with ER-positive BC ($P = 0.015$); patients with low Ki-67 (< 20%) had a median age of 54.7 (range: 27–79) years, *vs.* 49.5 (range: 26–74) years in those with high Ki-67 ($\geq 20\%$) ($P = 0.014$).

3.2. Prevalence of symptoms associated with phlegm-damp

Analysis of the prevalence of symptoms associated with phlegm-damp (questions 17–37, Table S2) demonstrated that the most common symptoms were a sensation of phlegm in the throat and/or hoarseness (23.2%), chronic rhinitis and/or sinusitis (21.9%), uterine myoma (21.3%), learning/attention/concentration difficulties (20.0%), and vaginal discharge (17.4%) (Table 3).

Table 2
Baseline patient and tumor characteristics ($N = 155$).

Characteristic	Number of patients	%
Median (range) age, year	52 (26–79)	
Motherhood status		
Yes	147	95
No	8	5
Histology		
Invasive ductal carcinoma	142	92
Invasive lobular carcinoma	11	7
Other/unknown	2	1
Tumor grade category		
Grade 1	8	5
Grade 2	48	31
Grade 3	56	36
Not available	43	28
ER status		
0	43	28
> 0 and < 1	4	3
$\geq$ 1 and < 2	19	12
$\geq$ 2 and < 3	46	30
3	40	26
Not available	3	2
PR status		
0	81	52
> 0 and < 1	18	12
$\geq$ 1 and < 2	25	16
$\geq$ 2 and < 3	15	10
3	13	8
Not available	3	2
HER2 status		
0	74	48
1	25	16
2	22	14
3	31	20
Not available	3	2
Ki-67 levels		
< 12%	38	25
12%–20%	16	10
$\geq$ 20%	81	52
Not available	20	13

ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; PR: progesterone receptor.

Table 3
Prevalence of symptoms associated with phlegm-damp, as reported by the patients (see Table S2, questions 17–37) ($N = 155$).

Symptom/pathology	Number of patients	%
Chronic rhinitis and/or sinusitis	34	21.9
A sensation of phlegm in your throat and/or hoarseness	36	23.2
Vaginal discharge	27	17.4
Learning/attention/concentration difficulties*	31	20.0
Uterine myoma*	33	21.3
Ovarian cyst: right ovary*	11	7.1
Ovarian cyst: left ovary*	9	5.8
Polycystic ovary*	4	2.6
Breast cyst: right breast*	11	7.1
Breast cyst: left breast*	20	12.9
Hypo/Hyper thyroid*	24	15.5
Any other endocrine system's malfunction*	8	5.2
Disturbed thinking, obsessive thinking/obsessive compulsive disorder*	16	10.3
Kidney stones: right kidney*	5	3.2
Kidney stones: left kidney*	4	2.6
Gall bladder stones and/or gall bladder had been removed*	11	7.1
High cholesterol levels under the age of 40*	17	11.0
Any auto-immune disease*	11	7.1
An under-skin nodules that can be felt*	5	3.2
A prolonged cough followed by phlegm expectorant	21	13.5
A feeling that something like a plum seed was stuck in your throat*	18	11.6

*Pathologies may result from "high-lipid Qi-like microscopic phlegm" and phlegm-damp which was not discharged.

3.3. Associations between the study parameters (emotional, CM-related, tumor markers)

In the preliminary step, the reliability coefficients, as measured with α-Cronbach, were 0.740 for patient's sensation of failing to perform their motherhood functions, 0.8 for patient's lack of self-fulfillment sensation, 0.783 for patient's behavioral tendency to avoid negative emotions, and 0.909 for patient's behavioral tendency to avoid negative relationships. The four components revealed by the PCA explained 69% of the total variances (31%, 18%, 11%, and 9%, respectively) (Table 4). Interpretation of the data was mostly consistent with the concepts covered by the scaled parts of the questionnaire. Table 5 presents the results of the analysis of the association between the parameters (logistic regression), where statistically significant associations were identified. As may be expected, significant associations were found between the EMs (sense of motherhood failure [EM1] and lack of self-fulfillment [EM2], $P < 0.001$). In addition, statistically significant associations were found between EMs and emotional repression, behavioral tendencies, and physical symptoms based on the CM, specifically, between sense of motherhood failure (EM1) and the markers associated with "high-lipid Qi-like microscopic phlegm" (RM3) ($P = 0.003$), and between physical symptoms of lack of self-fulfillment (EM3) and pain and phlegm-damp (RM1 + 2 and RM1) ($P < 0.001$). Statistically significant associations were found between RM variables associated with physical symptoms of emotional repression/"high-lipid Qi-like microscopic phlegm" (RM2) and avoiding behavior/"high-lipid Qi-like microscopic phlegm" (RM3 and RM4) and tumor parameters including grade, PR, and Ki-67 (RM2 and grade, $P = 0.022$; RM4 and grade, $P = 0.025$; RM2 and PR, $P = 0.047$; RM3 and Ki-67, $P = 0.027$). Patients with higher "high-lipid Qi-like microscopic phlegm" were more likely to have tumors with worse prognosis (PR-negative, higher grade, and higher Ki-67). As suspected, a statistically significant association was found between traumatic imprint (EM4) and PR (EM4 was found to be associated with PR negativity; $P = 0.036$). None of the variables in the study demonstrated significant association with ER or HER2 status.

4. Discussion

In this study, we showed statistically significant associations between emotional parameters, parameters related to repression of negative emotions and traumatic imprint according to CM, and

Table 4
Rotated component coefficients derived from principal component analysis.

Marker	Rotated component coefficient				
	Question (as in Table S2)	Component			
		1	2	3	4
EM1/RM3	6a/40a	0.968	0.035	0.030	0.098
EM1/RM3	6/40	0.968	0.035	0.030	0.098
EM1	5a	0.879	0.132	0.184	−0.003
EM1	5	0.875	0.124	0.181	−0.010
EM1	1	0.032	0.760	−0.092	−0.075
EM2	8a	−0.117	0.732	0.065	0.196
EM1	1a	0.047	0.710	−0.147	−0.130
EM2	8	−0.143	0.710	0.048	0.355
EM2	7a	0.185	0.693	0.119	−0.091
EM2	7	0.229	0.668	0.108	−0.111
RM3	41a	0.156	0.534	0.457	0.348
RM3	41	0.176	0.532	0.459	0.306
RM4	42	0.156	0.013	0.772	0.079
RM4	42a	0.200	−0.041	0.757	0.061
EM1	4	0.071	0.073	0.128	0.760
EM1	4a	0.010	0.020	0.157	0.753
EM1	3a	0.185	−0.085	−0.491	0.595
EM1	3	0.195	−0.084	−0.533	0.558

*Questions 2 and 2a in Table S2 were excluded from the principal component analysis as 95% of patients were mothers. EM: emotional marker; RM: Repression marker.

Table 5
Analysis (logistic regression) of the associations between the study variables.

N	Variables measured	OR (95% CI)	*P* value	Association description
152	RM2, PR	3.0 [1.0, 8.7]	0.047	Higher tendency to suffer from physical pains is associated with higher incidence of negative PR BC phenotype
110	RM2, grade	8.1 [1.3, 48.8]	0.022	Higher tendency to suffer from physical pains is associated with higher incidence of high-grade BC
116	RM3, RM4	3.9 [1.2, 12.9]	0.023	Both higher "high-lipid Qi-like microscopic phlegm" depositions are associated with each other
135	RM3, Ki-67	2.7 [1.1, 6.5]	0.027	Higher "high-lipid Qi-like microscopic phlegm" deposition is associated with high-Ki-67 BC
85	RM4, grade	2.7 [1.0, 7.4]	0.025	Higher "high-lipid Qi-like microscopic phlegm" deposition is associated with high-grade BC
155	EM1, RM3	10.3 [2.3, 46.3]	0.003	An intense sense of motherhood failure is associated with higher "high-lipid Qi-like microscopic phlegm" deposition
155	RM3, EM2	9.8 [2.2, 44.2]	0.003	"High-lipid Qi-like microscopic phlegm" is associated with an intense lack of self-fulfillment
155	EM2, EM1	10.0 [3.8, 26.4]	< 0.001	An intense lack of self-fulfillment sensation is associated with intense sense of motherhood failure
155	EM3, RM1 + 2	14.8 [4.1, 53.0]	< 0.001	An intense lack of self-fulfillment sensation psychosomatic symptoms is associated with physical pains and many phlegm-damp
155	RM1, EM3	41.2 [5.3, 318.2]	< 0.001	An intense lack of self-fulfillment sensation psychosomatic symptoms is associated with many phlegm-damp
152	EM4, PR	2.0 [1.04, 3.90]	0.036	Trauma is associated with PR negativity

Only statistically significant associations ($P < 0.05$) are presented. BC: breast cancer; CI: confidence interval; EM: emotional marker; OR: odds ratio; PR: progesterone receptor; RM: repression marker.

tumor biomarkers in BC patients. As far as we know, there is not enough evidence to suggest that negative emotions contribute to BC, although some evidence does suggest that trauma is associated with elevated BC occurrence [3,4]. In this study, we used the unique concepts of CM, phlegm, Qi stagnation, and meridian theory to bridge the gap between negative emotions and BC. The current CM scientific literature does link phlegm syndromes with physiological changes that may contribute to cancer pathogenesis, and also links phlegm syndromes with an aggressive type of BC and worse prognosis [8,9,12,14,26–29]. However, these studies do not suggest a mind-body linkage between repressed emotions, phlegm, Qi stagnation, and BC, and do not propose that unconscious intelligence may be a source of phlegm and Qi stagnation production. Thus, this study in its cross-disciplinary novel mind-body approach provides a framework for understanding how negative emotions and trauma contribute to BC pathogenesis. Our study also confirms prior studies on phlegm syndromes and their associations with physiological changes that may contribute to BC pathogenesis and particularly to that of aggressive BC subtypes [8,9,12,14,26–29].

We hypothesized that a patient's repression of negative emotions and the imprint of traumatic events requires certain physiological changes within psychological and anatomical barriers. We suggest that "high-lipid Qi-like microscopic phlegm" deposition within such barriers allows for sorting and buffering capabilities which are needed for this emotional repression. Our novel definition of CM "non-substantial phlegm" as "high-lipid Qi-like microscopic phlegm" may provide a scientific trackable physiological link between emotional imbalance, phlegm, Qi stagnation, and cellular molecular mechanisms.

Our results suggest that patients' repression of negative emotions evoked by their feeling of failure in performing motherhood duties and lacking a sense of self-fulfillment may not contribute directly to BC pathogenesis, rather that the patients' response to difficult emotions is associated with phlegm and stagnant Qi deposition within barriers (such as cellular membrane), thus leading to physiological changes that may be involved with BC development and could contribute to the development of a more aggressive BC type.

To date, there is no existence of ideas within the CM literature that consider patients' phlegm discharge symptoms and pathologies (such as rhinitis) as a means to discharge excessive phlegm that is produced to mask undesirable repressed emotions, nor view it as a positive mechanism for reducing health risks associated with phlegm accumulation [30]. Our study is novel to suggest that discharge of phlegm can be viewed as a reasonable physiological response for reducing such risks. Notably, using phlegm as an emotional defensive mechanism may be a natural positive reflex in the short run; however, with time it could become pathological.

The associations demonstrated in this study support our theoretical and clinical model. Since it has been suggested that there is a latency period between stress exposure and BC diagnosis [2], the questions refer to past emotions and events within the patients' memory. This can also serve as a tool to be used by healthy individuals as guidance for a preventative approach, and by practitioners in mind-body medicine in their evaluation process. Specifically, evaluation of patients' phlegm, Qi stagnation, and barrier status can be used as a reflection of negative emotions and trauma repression intensity. Raising awareness of this model to patients and providing outlets for repressed negative emotions and traumatic imprints, could therefore support disease prevention as well as be a form of treatment (although it may be challenging or inappropriate for some patients already diagnosed with cancer, particularly in advanced stages, or in patients undergoing already-difficult cancer treatments).

Our study is limited by the questionnaire used, which has not been validated. Nonetheless, the reliability of the questionnaire, as measured by α-Cronbach coefficient, and the multiple associations identified suggest that this novel questionnaire is worth further optimization and investigation. Notably, a few questions in our questionnaire appear in more than one cluster, as they can reflect more than one etiology. Our study is also limited by the parameters evaluated. In future studies, incorporating blood lipid parameters may be considered given the known association between these parameters and phlegm syndromes [10,11], and the association shown here between "high-lipid Qi-like microscopic phlegm" deposition and characteristics of poor BC prognosis.

5. Conclusion

The current study demonstrates the statistically significant relationship between emotional parameters (negative emotions, traumatic imprint and their repression), CM parameters, and oncologic parameters in BC. Higher intensity of negative emotions and trauma repression are associated with tumor characteristics related to worse prognosis. Additional research is warranted to further validate the questionnaire and to advance the understanding of the suggested model and its eventual impact on clinical practice.

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Authors' contribution

OB designed the study hypothesis and developed the study methodology, performed the analysis and drafted the manuscript. IT participated in drafting the manuscript. OB, VN and IT participated in data analysis and interpretation of data. OB, MWB, MF and CSZ participated in acquisition of data. OB, VN and MF supervised the study and provided administrative and material support. All authors contributed to the scientific discussion of the data and of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joim.2021.11.005.

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