

The effects of spiritual intervention and changes in dopamine receptor gene expression in breast cancer patients

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Abstract Breast cancer is the most common cancer in females in Iran and in most of the developed countries. Studies have shown that having chronic stress in individuals predisposes several types of cancer including breast cancer. Research results showed that spiritual factors correlate with indices of physical consequences such as heart disease, cancer, and death, so do psychiatric conditions and changes in receptor gene expression in depression, anxiety, and social dysfunction. Different studies demonstrated the role of neurotransmitters in occurrence and progression of cancers. They affected cells by their various types of receptors. An effective gene in mental and physical conditions is Dopamine receptor. Accordingly, the study was conducted to evaluate effects of psychotherapy (spiritual intervention) on changes in Dopamine receptor gene expressions in breast cancer patients. 90 female volunteers, including 30 healthy individuals and 60 diagnosed with breast cancer, considering exclusion criteria, were selected

for the purpose of the study. The breast cancer patients were further categorized into experimental and control groups of 30 each. Blood samples were collected both prior to and following the spiritual intervention to analyze changes in their dopamine gene receptor expressions. We observed that DRD2–DRD4 in the control group (breast cancer patients) PBMC increased compared to healthy individuals. Also, DRD2–DRD4 in intervention group PBMC decreased compared to the control group and to even lower than those of healthy individuals. The findings were of great significance in management and treatment of cancer because they revealed the possibility of using alternative treatments (e.g., spiritual interventions) apart from conventional medical treatments.

Keywords Breast cancer · Dopamine receptors · Gene expression · Spiritual intervention

Introduction

Cancer has turned to be one of the most prevalent health hazards globally. Among the various types, breast cancer is the most common one in women and also is the main cause of cancer mortality in women aged 40–44 years [1]. Experimental and clinical studies have shown that the chronic stress and impaired mental and spiritual conditions of each individual predispose several types of cancer including breast cancer [2–6]. In recent years, there has been overwhelming evidence to point out the effects of religion/spirituality on mental and physical health [7]. Approximately 40 years ago, religion, spirituality, and health reemerged in the body of literature on healthcare followed by an extensive increase in the turn of the century especially in the last 3 years (2009–2012) in which they

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rose to almost seven times as much [5]. World Health Organization Classification of Diseases added a spiritual dimension to the already existing indicators of health (bio-, psycho-, and social health).

Rapidly growing evidence shows that stress, negative feelings, and lack of spirituality, such as depression and anxiety, have adverse side effects on physiological systems which are necessary to maintain physical health and increase susceptibility to a wide range of physical disorders that ultimately lead to reduced life expectancy and quality of life [8, 9]. Therefore, R/S resources are important for cancer patients' coping, relief, anxiety, improving quality of life and interpersonal support [10].

Focus on gene expression allows for behavior and psychopathology to be examined based on the most basic unit of human body: cell [11]. Relation between psychological status and changes in various gene expressions in depression, anxiety, and social isolation has been confirmed [12]. Research has shown that changes in gene expressions are involved in many physiological events and psychological states of the individuals [13]. The changes in gene expression mediated by hormones and catecholamine can dysregulate immune function. Furthermore, environmental factors like stress can lead to the disruption of the balance between central nervous system and immune system [14]. Evidence of different types of diseases, such as breast cancer can be straight forward to chronic stress [15, 16]. The existence of several neurotransmitters may lead to tumor progression via stimulating the migration and dissemination of tumor cells to distant sites [17]. One of these neurotransmitters, Dopamine, has proliferative effects in nontransformed cells [17, 18]. Basu et al. showed that the reaction to stressful events is a significant increase in Dopamine levels [19]. Also, some studies indicated that Dopamine was related to growth diminution in some stomach, colon, and breast cancer tumors [17, 18].

Neurotransmitters affect different types of cells via their various receptors. Dopamine receptors are of five sub-categories, namely, D1, D2, D3, D4, and D5 where D1 and D5 are from D1-like family with stimulating properties; in contrast, D2, D3, and D4 receptors are from D2-like receptor family with inhibitory and anti-proliferative features. Dopamine receptors are from G-protein family containing D1 and D2 families' receptors. Both D1 and D5 receptors are members of D1-like family which are stimulators (excitatory) and induce cell proliferation. In contrast, D2–D4 receptors, members of D2-like receptor family, have antiproliferative properties [19, 20]. These receptors are either inductive or inhibitive that cause growth, proliferation or induce cell apoptosis, depending on the types of the receptors. In addition, research shows that in different diseases the gene receptor expressions

demonstrate various behaviors. For instance, in schizophrenia significant elevation was observed in D2 and D3 gene expression [21, 22]. In arthritis rheumatoid, the gene expressions of D2 and D4 receptors decreased and elevated, respectively. Jafari et al. showed that gene expression of D4 was elevated in lupus erythematosus [23]. Also, some other studies showed evidence of gene expression alterations in other diseases including Parkinson [24]. Pornour et al. showed that the expression rates of DRD1–DRD4 in PBMC of breast cancer patients have increased significantly compared to PBMC healthy people [25]. Regarding the important impact of chronic stress on Dopamine and its effects on occurrence and progression of breast cancer, the study of improvement effects of spiritual intervention on breast cancer patients is, without a doubt, necessary. Thus, this study was conducted to evaluate Dopamine receptor gene expressions after spiritual intervention in breast cancer patients and to compare Dopamine receptor gene expressions to those of a healthy sample.

Materials and methods

Participants

This research was conducted in 2012–2014 based on the experimental procedure by a pre-, post-test approach with two control groups. The population studied here included patients with breast cancer at Shohada Hospital in Cancer Research Center (C.R.C.) and Azar Clinic. The subjects underwent a similar conventional treatment procedure. They have been treated with surgery, chemotherapy, or radiation therapy as required, with at least 1 month gap from their complete treatment. Subjects with HER2 positive in both experimental and control groups received anti-HER2 therapy (Trastuzumab) and subjects with steroid receptors (ER+, PR+) received a resembling hormonal therapy in both groups (e.g., premenopausal subjects received Tamoxifen, and post-menopausal ones received Aromatase inhibitors). The sample was composed of volunteers with an age range of between 30 and 65 years, with one patient aged 25, and minimum literacy was required. They were fully informed prior to the study, and all signed a consent form. Women who reported, in a clinical interview, a history of psychotropic drug use during the 3 months before the study, had used alcohol or smoked, or those with neurosis or psychosis, such as depression and schizophrenia, were not allowed to enter the study.

In this study, taking into consideration the previous research of Pornour et al. [25, 26] the sample size was estimated by using the following formula as 25 plus 5 as the safe margin against loss throughout the process:

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 (s_1^2 + s_2^2)}{\Delta^2}$$

$$= 0/5 \quad \beta = 0/8 \quad \Delta = 4$$

$$n = \frac{(8.5 * 2 * 64)}{16} = 68$$

$$n = \frac{(1.96 + 0/84)^2 * (2s_1^2)}{4^2} = 24.5 = 25$$

Thus, they were categorized randomly into 2 groups of nearly 30, one as the experimental intervention group (E) and the other as a control group (C1). The final results were also compared to those of a third group of 30 healthy individuals, obtained results of which were adapted from a study conducted by Pornour and his colleagues [25] as the second control group (hereafter labeled as C2) (Table 1).

Questionnaires

In the first part, the sociodemographic, clinical, pathological, and biological data were collected by a self-made questionnaire. Blood samples: to investigate the expression levels of genes in patients' blood samples, before and after the spiritual intervention sessions, 5 cc blood was obtained from participants. The control group (C1) was asked to stay for a period of 3 months on the waiting list. Furthermore, 30 participants (E) were randomly divided into two groups

and interventions simultaneously started. PBMCs (Peripheral Blood Mononuclear Cells) from collected samples were isolated using density gradient centrifuge by Ficoll-Hypaque (Pharmacia, Uppsala, Sweden) density centrifugation density of which was 1.077 ± 0.001 g/ml (20 °C) and its osmolality 290 ± 15 mosm. Total mRNA was extracted from PBMC. RT-PCR was performed to confirm the presence of different Dopamine receptors (DRD1–DRD5). To further investigate the health status of the sample in both experimental and control groups after screening, General Health Questionnaire (GHQ 28) was administered. GHQ is a screening instrument to identify psychological distress among adults in primary care settings [27]. The original version comprised 60 items, and subsequently various versions of different length have been constructed and validated (30-item, 28-item, 20-item, and 12-item versions). The present study made use of the 28-item version.

The study also took advantage of the Paloutzian & Ellison spiritual well-being questionnaire which is a 20-item measure that assesses perceptions of spiritual quality of life [28]. The measure includes two subscales: [1] religious well-being and [2] existential well-being. It was applied to measure the spiritual well-being status of the participants to evaluate the effectiveness of the spiritual intervention in the study.

It is worth mentioning that the spiritual well-being and GHQ 28 questionnaires were administered on the day the blood samples were collected before and after the therapy:

Table 1 The demographic, pathological, and biological characteristics of the study sample

	Experimental group	Control group 1	Total (E + C1)	Healthy group (C2)
Age				
Mean	51.88	47.23		49.33
N	29	28	57	30
Marital status				25
Married	21	20	41	
Widowed/divorced	5	4	9	2
Never married	3	4	7	3
Stage				
Stage 1	7	9	16	
Stage 2	17	14	31	
Stage 3	5	5	10	
Grade				
Grade 1	1	2	3	
Grade 2	11	13	24	
Grade 3	17	13	30	
Biomarkers				
(+)ER	16	16	32	
(+)PR	9	10	19	
(+)HER2	6	4	10	

the data were collected 1 week prior to the therapy and was repeated 1 week after the end of therapy.

Statistical analysis

Subsequent to CYCLE THRESHOLD determination for each blood sample, LINREG software was applied to investigate the florescent rate for each blood sample in participants.

Efficiency of each reaction was determined precisely by the software. Real-time PCR data were analyzed by Rest 2005 & 2009 software (an independent software program employed to study gene expression by amplification data). The obtained results and demographic data were analyzed by means of SPSS software. Also, the relationship significant value in this study was less than 0.05 ($P < 0.05$).

In the statistical analysis of the results, subjects' means of scores in pre- and post-test were calculated. Then, in order to verify the hypotheses put forward in the study and to compare the two groups (experimental and control), a covariance analysis was performed regardless of primary differences.

Procedure

To start with, blood samples were collected from all the groups (E, C1, and C2) which were genetically studied (for further information on the genetic analysis see [25, 26]).

Next, GHQ (General Health Questionnaire) was applied to all groups both prior to and after the spiritual intervention (a 3 month interval) to identify the effects of the treatment on the levels of psychological distress in individuals. Furthermore, the Paloutzian & Ellison spiritual well-being questionnaire was administered to all participants before and after the spiritual intervention with the same time interval as GHQ.

Once the questionnaires were filled in by all participants, the experimental group (E) was administered a set of spiritual intervention sessions in the Cancer Research Center at Shahid Beheshti University of Medical Sciences. The sessions were held by two psychologists as "instructors". The package included 10*120 min sessions of group therapy under observing the regulations of the procedures in such treatments. The topics discussed were generally extracted from similar studies (e.g., [10, 29–36]) which encompassed topics such as the concept of death, forgiveness, pray, altruism, and thankfulness. These concepts are generally accepted by most of Unitarian religions. Spiritual experts were also consulted on the concepts to be discussed in the treatment. The topics were calibrated to the target culture of the participants and the purposes of the study. Table 2 clearly depicts the topics in each session and the assigned homework. To filter any uncontrolled effect

by the psychologist performances in the sessions, all sessions were held by the two psychologists simultaneously. Also, to facilitate communication and avoid potential distractions, the seat arrangement was in a u-shape setting headed by the psychologists.

Results

The findings revealed that there was a significant difference (proved through measures of normality test, homogeneity of covariance, and homogeneity of regression) in general health (GHQ) and spiritual well-being (Paloutzian & Ellison) post-test means in the two groups (E & C1) after controlling the effect of pre-test. Covariance analysis results are depicted in Table 3. It is noteworthy that 17 of the questionnaire responses (10 in the pre-test and 7 in the post-test) were incomplete; therefore, omitted from analysis.

As shown in Table 3, with omission of the effect of pre-test variable and with regard to the calculated F, it is observed that there is a significant difference in adjusted means of participants general health scores based on the group they belong to (E or C1) in post-test ($P < 0.05$).

As shown in Table 4, with omission of the effect of pre-test variable and with regard to the calculated F, it is observed that there is a significant difference in adjusted means of participants spiritual well-being scores based on the group they belong to (E or C1) in post-test ($P < 0.05$). The effect size calculated was 0.54, this means 54 % of total variance or individual variations in participants have changed as a result of the spiritual intervention. Also, Table 5 gives information on Dopamine gene receptors' changes prior to and after the intervention in the experimental group.

In this study, expressions of different types of Dopamine receptor genes were evaluated in breast cancer patients' PBMC, in those who received the intervention and in those who did not, (before and after intervention) and were additionally compared to those of healthy individuals' PBMCs. The results of RT-PCR showed that all types of Dopamine receptors were expressed in PBMCs of breast cancer and healthy individuals [25, 26], with the difference observed in the genes expression rates (as shown in our pilot study [25], the Dopamine gene expression rates were significantly higher than those of healthy individuals).

The findings revealed that after the spiritual intervention cancer patients as compared to their initial status and those of the control group (C1) showed a significant reduction in gene receptor expressions of DRD1, DRD2, DRD3, DRD4, and even DRD5 by 8.9, 10.7, 11.8, 8.9, 9.7, and 3.7 respectively. This clearly emphasizes the efficiency of spiritual intervention in significant reduction of these receptors expressions.

Table 2 A session-based representation of the spiritual intervention

Session	Topic	Group work	Homework	Remarks
1	Introduction	–	–	A description of the procedure of the group therapy and the rules governing the sessions was given
2	Elicitation of Spirituality	Discussion of the possible meanings of spirituality and its necessity	Listing the personal cases of spiritual experiences in their past life	–
3	Self-observation and meditation	Meditation	Daily meditation and expressing feelings of spiritual experiences	The group was trained how to mediate in a practice in the session
4	Examining the effects of self-observation and meditation	Reporting their weekly experiences and group meditation	Same as before	–
5	Death and immortality	Discussion on death and their experiences of losing loved ones	Reflecting on death in nature	The purpose was to neutralize the fear of death, to introduce it as a stage in life cycle, and to establish death as a new beginning
6	Prayer and forgiveness	Discussing the effects and practice of forgiveness on their spiritual well-being	Meditation was followed by a prayer asking forgiveness for self and others who bothered them. They were asked to randomly and blindly pray for the other members of the group	Participants prayed, “oh Lord, I forgive those who have annoyed me. Forgive them as I have forgiven them. Thus bestow me with your forgiveness”
7	Anger management and altruism	Discuss the disadvantages of anger and random acts of kindness	Listing their random acts of kindness and cases of successful anger management	The acts of kindness could range from as simple as giving a call to a friend to donations made to the needy
8	Patience and reliance	Discussion on the nature of patience and effects of reliance on a spiritual power (God)	Listing their unpleasant feelings a in hardships especially the most recent ones	Patience was introduced as belief in time and passage of time. They were instructed on the concept “this too shall pass”
9	Thankfulness and giving	Discussing their blessings in current life	Listing personal blessings	The concept of “enjoying what you have” was established leading to giving and kindness
10	Final session	Reporting spiritual experiences, possible effects, and satisfaction	–	–

Table 3 The effect of spiritual intervention on general health

Source	SS	df	MS	<i>F</i>	Sig	Effect size	Observed power
Pre-test	413.12	1	413.12	17.56	0.001	0.32	0.98
Group	383.26	1	383.26	16.29	0.001	0.31	0.97
Error	870.48	37	23.52				
Total	63,868	40					

Table 4 The effect of spiritual intervention on spiritual well-being

Source	SS	df	MS	<i>F</i>	Sig	Effect size	Observed power
Pre-test	160.26	1	160.26	11.58	0.002	0.23	0.91
Group	1076.19	1	1076.19	77.78	0.001	0.54	0.99
Error	511.93	37	13.83				
Total	151,186	40					

Table 5 E PBMC pre-test scores compared to post-test scores

Genes receptors	P value	Rate of change	Standard error
Dopamine receptors			
DRD1	0.001***	9.8	1.7
DRD2	0.001***	8.1	0.89
DRD3	0.001***	8.55	0.96
DRD4	0.001***	6.94	0.72
DRD5	0.045*	2.56	0.63

*** Significant decreasing at $P \leq 0.001$ level (down regulation)** Significant decreasing at $P \leq 0.01$ level (down regulation)* Significant decreasing at $P \leq 0.05$ level (down regulation)**Table 6** E PBMC compared to C1 PBMC DRD1–DRD5 genes expression

Genes receptors	P value	Rate of change	Standard error
Dopamine receptors			
DRD1	0.001***	8.6	±0.845
DRD2	0.001***	10.73	±0.771
DRD3	0.001***	11.8	±1.01
DRD4	0.001***	8.9	±0.76
DRD5	0.004**	3.7	±0.73

*** Significant decreasing at $P \leq 0.001$ level (down regulation)** Significant decreasing at $P \leq 0.01$ level (down regulation)* Significant decreasing at $P \leq 0.05$ level (down regulation)

The results as stated in Table 1 showed that there was a significant reduction in gene receptor expressions in the experimental group (E) compared to control group (C1) (Tables 6, 7).

Observations made following the spiritual intervention showed that there was a significant decrease in gene receptor expressions of DRD1, DRD2, DRD3, DRD4, and DRD5 by 2.73, 4.53, 7.36, 2.44, and 3.62 respectively in cancer patients (E) who underwent the spiritual intervention compared to healthy individuals (C2).

The biological, pathological, and demographic analysis of the data obtained from cancer patients with the results of gene receptors expression showed that there is a direct correlation between DRD2 receptor increase and the stage of the disease. There was not a distinct correlation among ER, PR, Her2, and patients' age.

Discussion

Studies conducted recently revealed that Dopamine gene receptor expression patterns in patients suffering from chronic stress vary in different diseases: Schizophrenia, Lupus Erythematosus, Psoriasis, Parkinson, and lung cancer

Table 7 E compared to C2, DRD1–DRD5 genes expressions in breast cancer patients

Genes receptors	P value	Rate of change	Standard error
Dopamine receptors			
DRD1	0.006**	2.73	±0.45
DRD2	0.001***	4.53	±0.54
DRD3	0.001***	7.36	±0.83
DRD4	0.027*	2.45	±0.52
DRD5	0.01**	3.63	±0.58

*** Significant decreasing at $P \leq 0.001$ level (down regulation)** Significant decreasing at $P \leq 0.01$ level (down regulation)* Significant decreasing at $P \leq 0.05$ level (down regulation)

to mention a few examples [20–23]. Back in 1990, Seeman et al. observed changes in Dopamine gene receptors in Parkinson patients [24]. Kwak and colleagues reported a substantial rise in D2 and D3 gene receptor expressions in PBC of Schizophrenia patients [22]. A study conducted by Sheikhpour et al. in 2012 showed a considerable reduction in D2–D4 receptor expressions [20].

Unlike other studies, in this innovative study, gene expression changes for these receptors in breast cancer patients increased, and it was particularly significant in D2 family. It is to bear in mind that given the previously mentioned findings, a substantial increase in inhibitor receptors can contribute to weakening of the immune system and, thus it can reduce the effectiveness of the system on excessive growth of cancer cells leading to the spread of the disease. The comparison of gene expression changes in blood cells of patients (E) with healthy individuals (C2) shows that Dopamine receptor genes DRD1–DRD4 significantly increased in the expression of these receptors in the patient's peripheral blood cells, which can reduce the number of immune cells, especially T cells. Reduction in T-cells, in turn, causes the cellular and humoral system to be weakened. Humoral system is weakened by reducing the production of cytokines such as TNF- α which is one of the factors that induce programmed cell death in cancer cells. Hence, a reduction in the number of T-cells is associated with decreased production of T cytokines such as NF- α which can most probably be proliferated by tumor cells in the absence of such cytokines [37]. Previous studies have shown that Dopamine has indirect effects on the growth of some cancer cells in the rats with breast and colon cancer [18].

The obtained results after the analysis of the data followed by the spiritual intervention are evidence for the reduction of Dopamine (DRD1–5) gene receptor expressions as compared to the control group (C1). To our surprise, the decrease mentioned earlier was even lower than

those of healthy individuals. The spiritual intervention lowered Dopamine (D2 family) gene receptors which, in turn, reinforced the immune system through an increase in the number of T cells, TNF- α producer. It seems that it restrains the consequences of chronic stress which was responsible for the raise in these gene expressions [37]. Thus, the body recovers its ability to inhibit the untamed growth of cancer cells. In other words, spiritual intervention gives the body an opportunity to inhibit the growth of cancer cells through restraining the increase in Dopamine gene receptor expressions. Due to the dual roll Dopamine receptors play (either as inducers or inhibitors) it should be mentioned that all dopamine receptors have expressions in PBMCs; receptors work in an orchestral form, and gene expression changes for each of them can alter the cells' behavior. However, the whole D2 families of genes have alteration in breast cancer patients and only D1 increased in those patients; as a result, increasing D2 families could cover D1 verification effects and have more effects on patients with PBMCs [25].

It was also hypothesized that there was a correlation between clinical, pathological, and biological data and Dopamine gene receptor expressions [25]. The results revealed that there was a significant relation between cancer stage and D2 gene receptor expressions. The possible explanation might be the fact that chronic stress, which leads to more dopamine gene receptor expressions, enhances the severity of the cancer. In other words, the spirituality will improve health status to protect patients by at least lowering the stage of the disease.

The previous studies showed the effectiveness of R/S on different kinds of diseases, especially cancer [2–6, 38, 39]. It seems that when people feel an attachment to a spiritual resource, the consequences of the disease cause lower degrees of fear and anxiety in them, and they experience fewer negative emotions. Furthermore, once the patients were inspired by resurfaced spiritual concepts such as forgiveness, patience, and thankfulness (sessions 6, 8, and 9), their lives turned out to be more meaningful. Reconstruction of some spiritual notions apparently altered their perspectives to their lives. For instance, re-establishment of death (session 5) led to a more positive attitude towards the end of life, as a transitional phase rather than a closing stage.

Eventually, based on the observations carried out in this study, performing the spiritual intervention, along with other types of treatments in breast cancer patients' recovery process, seems promising. In addition, DRD2 gene expression changes carry considerable potential as a further marker for the diagnosis of breast cancer, together with other diagnostic markers of breast cancer. Additional investigations on using D2 as a new therapeutic perspective are highly recommended. Also, this study could only focus

on dopamine gene receptor expressions. Other investigations are highly recommended to study the expressions of other genes. For instance, the authors of this study are currently conducting experiments on serotonin gene receptor expressions. There were some studies on antidepressant effects on cancer cells and cancer therapy. For example, some studies showed the apoptotic effects of D2 agonist in breast cancer cells and nonsmall cell lung cancer [20, 25, 40]; therefore, future studies are recommended to focus on the potential effects of antidepressants on preventing the aggravation of cancer.

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Compliance with ethical standards

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

References

1. Akbari A, Razzaghi Z, Homae F, Khayamzadeh M, Movahedi M, Akbari ME. Parity and breastfeeding are preventive measures against breast cancer in Iranian women. *Breast Cancer*. 2011;18(1):51–5.
2. Gall TL, Kristjansson E, Charbonneau C, Florack P. A longitudinal study on the role of spirituality in response to the diagnosis and treatment of breast cancer. *J Behav Med*. 2009;32(2):174–86.
3. Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nat Clin Pract Oncol*. 2008;5(8):466–75.
4. Daniels M, Merrill RM, Lyon JL, Stanford JB, White GL Jr. Associations between breast cancer risk factors and religious practices in Utah. *Prev Med*. 2004;38(1):28–38.
5. Ness PHV, Kasl SV, Jones BA. Religion, race, and breast cancer survival. *Int J Psychiatr Med*. 2003;33(4):357–75.
6. MacArthur AC, Le ND, Abanto ZU, Gallagher RP. Occupational female breast and reproductive cancer mortality in British Columbia, Canada, 1950–94. *Occup Med*. 2007;57(4):246–53.
7. Koenig HG. Religion, spirituality, and health: the research and clinical implications. *International Scholarly Research Notices*. 2012;2012.
8. Brown KW, Levy AR, Rosberger Z, Edgar L. Psychological distress and cancer survival: a follow-up 10 years after diagnosis. *Psychosom Med*. 2003;65(4):636–43.
9. Kubzansky LD, Thurston RC. Emotional vitality and incident coronary heart disease: benefits of healthy psychological functioning. *Arch Gen Psychiatry*. 2007;64(12):1393–401.
10. Koenig HG. Spirituality in patient care: why, how, when, and what. Philadelphia: Templeton Foundation Press; 2013.
11. Rutter M, Moffitt TE, Caspi A. Gene–environment interplay and psychopathology: multiple varieties but real effects. *J Child Psychol Psychiatry*. 2006;47(3–4):226–61.
12. Kawai T, Morita K, Masuda K, Nishida K, Shikishima M, Ohta M, et al. Gene expression signature in peripheral blood cells from

- medical students exposed to chronic psychological stress. *Biol Psychol*. 2007;76(3):147–55.
13. Feinstein D, Church D. Modulating gene expression through psychotherapy: the contribution of noninvasive somatic interventions. *Rev Gen Psychol*. 2010;14(4):283.
 14. Black PH. Central nervous system-immune system interactions: psychoneuroendocrinology of stress and its immune consequences. *Antimicrob Agents Chemother*. 1994;38(1):1–6.
 15. Jacobs JR, Bovasso GB. Early and chronic stress and their relation to breast cancer. *Psychol Med*. 2000;30(03):669–78.
 16. Solomon GF. Psychoneuroimmunology: interactions between central nervous system and immune system. *J Neurosci Res*. 1987;18(1):1–9.
 17. Mancino M, Ametller E, Gascón P, Almendro V. The neuronal influence on tumor progression. *Biochim Biophys Acta*. 2011;1816(2):105–18.
 18. Chakroborty D, Sarkar C, Mitra RB, Banerjee S, Dasgupta PS, Basu S. Depleted dopamine in gastric cancer tissues dopamine treatment retards growth of gastric cancer by inhibiting angiogenesis. *Clin Cancer Res*. 2004;10(13):4349–56.
 19. Basu S, Nagy JA, Pal S, Vasile E, Eckelhoefer IA, Bliss VS, et al. The neurotransmitter dopamine inhibits angiogenesis induced by vascular permeability factor/vascular endothelial growth factor. *Nat Med*. 2001;7(5):569–74.
 20. Shaikhpour MAS. Significant changes in D2-like dopamine gene receptors expression associated with non-small-cell lung cancer: could it be of potential use in the design of future therapeutic strategies? *Curr Cancer Ther Rev*. 2012;8(4):304–10.
 21. Ilani T, Ben-Shachar D, Strous RD, Mazor M, Sheinkman A, Kotler M, et al. A peripheral marker for schizophrenia: increased levels of D3 dopamine receptor mRNA in blood lymphocytes. *Proc Natl Acad Sci*. 2001;98(2):625–8.
 22. Kwak YT, Koo M-S, Choi C-H, Sunwoo I. Change of dopamine receptor mRNA expression in lymphocyte of schizophrenic patients. *BMC Med Genet*. 2001;2(1):3.
 23. Jafari M, Ahangari G, Saberi M, Samangoui S, Torabi R, Zouali M. Distorted expression of dopamine receptor genes in systemic lupus erythematosus. *Immunobiology*. 2013;218(7):979–83.
 24. Seeman P, Niznik HB. Dopamine receptors and transporters in Parkinson's disease and schizophrenia. *FASEB J*. 1990;4(10):2737–44.
 25. Pornour M, Ahangari G, Hejazi SH, Deezagi A. New perspective therapy of breast cancer based on selective dopamine receptor D2 agonist and antagonist effects on MCF-7 cell line. *Recent Pat Anti-Cancer Drug Discov*. 2015;10(2):214–23.
 26. Hejazi SH, Ahangari G, Pornour M, Deezagi A, Aminzadeh S, Ahmadkhaniha HR, et al. Evaluation of gene expression changes of serotonin receptors, 5-HT3AR and 5-HT2AR as main stress factors in breast cancer patients. *Asian Pac J Cancer Prev*. 2013;15(11):4455–8.
 27. Goldberg D, Williams P. General Health Questionnaire. Hämtad från. 1991.
 28. Ellison LL. The spiritual well-being scale. 2006.
 29. Mueller PS, Plevak DJ, Rummans TA, editors. Religious involvement, spirituality, and medicine: implications for clinical practice. Mayo Clinic Proceedings; 2001: Elsevier.
 30. Shaw B, Han JY, Kim E, Gustafson D, Hawkins R, Cleary J, et al. Effects of prayer and religious expression within computer support groups on women with breast cancer. *Psycho-oncology*. 2007;16(7):676–87.
 31. Sawatzky R, Ratner PA, Chiu L. A meta-analysis of the relationship between spirituality and quality of life. *Soc Indic Res*. 2005;72(2):153–88.
 32. Grant E, Murray SA, Kendall M, Boyd K, Tilley S, Ryan D. Spiritual issues and needs: perspectives from patients with advanced cancer and nonmalignant disease. A qualitative study. *Palliat Support Care*. 2004;2(04):371–8.
 33. Meraviglia M, editor Effects of spirituality in breast cancer survivors. *Oncology Nursing Forum*; 2006: Oncol Nurs Society.
 34. Peterman AH, Fitchett G, Brady MJ, Hernandez L, Cella D. Measuring spiritual well-being in people with cancer: the functional assessment of chronic illness therapy—spiritual well-being scale (FACIT-Sp). *Ann Behav Med*. 2002;24(1):49–58.
 35. Greer S, Moorey S, Baruch J, Watson M, Robertson BM, Mason A, et al. Adjuvant psychological therapy for patients with cancer: a prospective randomised trial. *Brit Med J*. 1992;304(6828):675.
 36. Lee MM, Lin SS, Wrensch MR, Adler SR, Eisenberg D. Alternative therapies used by women with breast cancer in four ethnic populations. *J Natl Cancer Inst*. 2000;92(1):42–7.
 37. McKenna F, McLaughlin P, Lewis B, Sibbring G, Cummmerson J, Bowen-Jones D, et al. Dopamine receptor expression on human T-and B-lymphocytes, monocytes, neutrophils, eosinophils and NK cells: a flow cytometric study. *J Neuroimmunol*. 2002;132(1):34–40.
 38. Keegan T, Chang ET, John EM, Horn-Ross PL, Wrensch MR, Glaser SL, et al. Recent changes in breast cancer incidence and risk factor prevalence in San Francisco Bay area and California women: 1988 to 2004. *Breast Cancer Res*. 2007;9(5):R62.
 39. Schnall E, Wassertheil-Smoller S, Swencionis C, Zemon V, Tinker L, O'Sullivan MJ, et al. The relationship between religion and cardiovascular outcomes and all-cause mortality in the Women's Health Initiative Observational Study. *Psychol Health*. 2010;25(2):249–63.
 40. Bhatia M, Collins T, Sachlos E, Risueno RM. Treatment of cancer with dopamine receptor antagonists. Google Patents; 2012.