FULL PAPER

The Feasibility of psychological Upsets Admittance in Breast Cancer Risk Factors Index

Prepared by

Harith S. H. Al-rekabi
General surgeon
Al-kindy Teaching Hospital
Ministry of health /Iraq
harith_salman@yahoo.co.uk

Zuhair Basheer Kamal
Prof. General surgeon
Al-kindy College of Medicine
University of Baghdad /Iraq

Abstract

Background:
There are few books in the sense that mental disorders can be harmful or harmless to the risk factors for the progression of breast cancer; which may be related to a new perspective on alternative therapies that may include genetics, immunology associated with hormonal factors. The variety of these book reviews encourages breast doctors to see this correspondence of better results.

Objectives:
Confirming statistical evidence that the link between psychiatric disorders and breast cancer confirms new allegations in management

Patients and methods:
A retrospective case-control study of acute and chronic mental upset involving 620 breast patients from Jan. 2009 to Jan. 2020 halved equally in two groups, comparative survey between ages, gender, various psychiatric disorders, duration, histo-pathological type of breast cancer, and immunohistochemistry. Chi-square is designed individually to check the p value.

Results:
The statistical relationship between psychiatric disorders and breast cancer is determined by the negative link and its magnitude. Women are more likely to be affected than men with breast cancer apparently after fourteen years. Strong emotional response to PTSD (67.5%) of cases and Invasive ductal cell carcinoma is more common than other types .Fortunately (<15 %) account for positive HER2.

Conclusions:
Establishing this is associated with the need to adopt psychiatric disorders in a range of risk factors for breast cancer leading to increased better management.

Key words: Breast cancer. Mental disorders. Mathematical relationships.

Introduction:

Breast cancer makes up 27% of cancer in young women and is the second leading cause of cancer in about 15 percent of the United States. It remains a major cause of death and illness which indicates the need for continuous effort to better understand the test. The effort, use of preventive strategies, and the development of better treatment. Therefore, further understanding of the risk factors for cancer is a matter of concern because the incidence and mortality vary with different factors including race and ethnicity.

Hormones, lifestyle, and environmental factors can increase the risk of breast cancer. But it is not clear why some vulnerable people get cancer and other vulnerable people have never had it. It is possible that this cancer is caused by complex interactions between genes and environmental factors such as female genital mutilation, aging, and white women with multiple sclerosis; while American Africa has the highest mortality. Intrauterine weight at birth and height may take into account the risk factors associated with future breast cancer. Premature menstruation, late menstruation, late childbirth, and null parity also have the same legal effect while premature menstruation lowers circulating estrogen and reduces the level of interest and while prolonged breastfeeding reduces the risk of breast cancer.

Fatty acids and obesity increase the risk of breast cancer and reduce the incidence (9%) in those people who eat a low-fat diet and drink moderate alcohol can increase the risk of breast cancer by (2%) due to hormonal changes or due to effect of carcinogenic metabolite, and the reverse is true regarding decrease alcohol consumption; Active and passive smokers may increase the risk of cancer.

Family history holds (10%) of all cases of genetic breast cancer where the incidence is directly proportional to the affected numbers;

This risk increases between one or two generations especially when a person moves from a low-risk area to high-risk countries and when later developed the level tends to rise sharply, this difference explains the natural influences especially dietary fats and attitudes.

Stem cell formation (BCSCs) has a strange definition and is thought to be nidus in tumor genesis and metastasis and is resistant to chemo- and radiotherapy, which is also considered mandatory. Recurrence of the disease after treatment. BCSCs are the basis of plant complexity, as they are able to reproduce and cause cancer cells to cover most of the tumor.(Mansi Shah & Cinzia Allegrucci, 2012: 155-66)

Emulating theory (BCSCs), the emergence of clonal cells suggests that different clones of cancer cells come in different pressures and minimal environmental effects, which may include chronic and external factors. (Nowell PC,1976: 23–8). Transformed cell clones may accumulate when increased hyper proliferation is associated with genetic instability. Tumor heterogeneity is caused by genetic variation, as well as the growth of mutant cells that do not include stem cells. (Spencer SL, Albeck JG, Burke JM, Sorger PK,2009: 459). A tumor is the result of a series of random mutations and the emergence of clone cells that appear in growth resulting from activated oncogenes and / or genetically modified genes selected by Darwin's method.(Marusyk A, Almendro V, Polyak K,2012: 323–34).

The Psycho-physiological axis in breast cancer is still being investigated to determine if it is the cause or risk of oncogenesis that needs proper treatment and hopefully prevented. Among the

various types of mental disorders; stress that may be severe (temporary) or chronic (recurrent or long-lasting).(Chida y, hamer m,2008 : 829-85) **,** (Chrousos gp,2009 : 374-81) The exact mechanism is not fully understood but many speculations point to a chronic environment that can weaken the immune system causing diseases such as cancer and there is evidence that their function of both the immune system and the mutant plays a role in preventing recurrence for women with breast cancer. Lymphocytes and their cytokine release patterns are involved in both primary and secondary breast cancer; also, cancer prognosis may be related to the state of the immune system. The hypothesis that the immune system plays a leading role in the etiology of breast cancer is supported by epidemiologic, preclinical, and clinical research, as well as strong support for the view that immune status and immunomodulatory therapy play an important role in holistic treatment of breast cancer. (standish lj, sweet es , novak j, wenner ca, bridge c, nelson a, martzen m, torkelson c et al, 2008 : 158-68)

In addition, the main evidence is that stress hormones have similar effects of AMP-kinase inhibition that inhibit Anoikis (a specific type of programmed cell death) within normal mammary epithelial cells through a phospho-rich protein in astrocytes (PEA15) Ser116 phosphorylation. Therefore, inhibition of the axis of AMPK-PEA15 may prevent the spread of breast cancer and metastasis. (Sravanth k Hindupur, Sai A balaji, Meera Saxena, Shubham Pandey1,Gopalkrishnashetty Sreenivasmurthy Sravan, Namrata Heda et al,2014: 16 :420)

Chronic stress has also been shown to indicate high levels of IL-6 circulation that increase blood supply that can accelerate tumor growth and angiogenesis. (Nilsson mb, langley rr, fidler ij.,2005 : 10794-800) , (WU S, Rodabaugh k, Martinez-mazao , Watson jm, Silberstein ds, Boyer cm, et al. ,1992 : :997-1007) , (Ell ok, nishimoto R, mediansky L, mantell J, hamovitch ,1992: 531-41)

The basics of cancer cell start are illustrated by GLEN RUSSELL and PUNA WAI ORA who found that chronic stress causes cancer and described it in stages where:

SECTION 1 OF THE COLLECTION: UNFORGETTABLE SHOCK:

 a person with "inevitable" or severe mental-emotional trauma, which affects deep sleep and melatonin production needs 18-24 months before the diagnosis of cancer because the hormone melatonin from the pineal gland inhibits the growth of cancer cells through interleukin 2 (IL-2).

SECTION 2 TERMS: ADRENALINE SUPPORT:

At the mitochondrial level, high cortisol may suppress adrenaline-induced glucose metabolism which produces low pH which causes the transformation of cancer-changing fungus into the next stage.

SECTION 3 CANCER: CANCER:

This yeast-like-fungus pleomorphism enters the nucleus to reproduce, releasing "mycotoxins", blocking DNA repair, tumor suppressor gene p53 and proto-oncogenes turn into oncogenes, causing cancer cell mutations.

SECTION 4 OF THE CANCER: NIACIN DEFICIENCY:

Decreased adrenaline also eliminates dopamine which is essential for tryptophan synthesis, the latter being needed for the synthesis of niacin / niacin amide (vitamin B3). Without niacin; cellular respiration is impaired due to glucose uptake which leads to cellular mutations and cancer.

SECTION 5 TERMS: VITAMIN C:

 Ascorbic acid (vitamin C) is used by dopamine to make noradrenaline which is converted into adrenaline in the adrenal glands. Also, it reduces the stressful effect of adrenaline on the heart and blood pressure systems and prevents cell DNA damage in chronic stress conditions; continued loss of ascorbic acid with depleted adrenaline increases mitochondrial DNA damage and mutation, resulting in the conversion of normal cells into cancer cells.

SECTION 6 OF THE COURT: CULTURAL PRESSURE:

High stress hormones reduce serotonin and dopamine levels in the brain causing internal depression — as a person with unavoidable shock and prolonged stress, which in turn inhibits the production of interleukin-2 that stops T cells, B cells, natural killer cells, macrophages. , and the functions of neutrophils. In addition to immune cells, yeast-like fungus has a pleomorphized that causes cancer cells and continues to multiply.(Graham J, ramirez A, love S, richards M, burgess C,2002 : 324)

Stress-neuroendocrine axis activation had a 30-fold increase in metastasis with β- Adrenergic stimulation with increasing penetration of CD11b + F4 / 80 + macrophages into the primary tumor and thus induced pro-metastatic gene expression associated with segregation of M2 macrophages. Treatment with β-antagonist propranolol reversed the entry of macrophage-induced stress and tumor that was prevented from spreading to distant tissues. The effects of stress on distant metastasis are also prevented by vivo macrophage suppression using (CSF-1 receptor kinase inhibitor GW2580). These neural regulators are novel breast cancer metastasis as well, propose new (anti-metastatic) therapeutic strategies targeting β-adrenergic pro-metastatic gene expression into primary breast cancer.

 A large meta-analysis of up to 131 studies linked chronic stress to increased breast cancer developed by the activity of a sympathetic nervous system that did not show a significant effect on primary growth but improved metastatic proliferation with effects on both primary growths metastasis and tumor cell extravasation / colonization of distant target tissues; the findings suggest that stress may contribute to the progression of cancer and link Beta-blocker use with reduced metastasis and breast cancer-related mortality.(Algazi M, plu-Bureau G, flahault A, dondon MG, le MG,2004 : 535–41).

Activating transcription factor (ATF3) in response to stress conditions in all cell types plays an important role in promoting breast cancer metastasis. The exposure of ATF3 to stromal cells, but not epithelial cancer cells, is associated with more severe clinical outcomes, and this gene, probably represents the major cause of cancer death and its spread. In addition (ATF3) stimulates the body's own cells to move around and provide the cancer with a way out of other parts of the body. This type of depression may one day work as a drug target to combat

cancer metastasis if additional studies produce these results, (Chris C. Wolford , stephen J. mc conoughey, swati P. Jalgaonkar , marino Leon, anand S. merchant et al ,2013 : 2754-3183) .

Cortisol directly affects the genesis of breast cancer by altering the generation or activity of estrogen with more evidence suggesting estrogen plays an important role in breast cancer etiology . (Henderson B, ross R, bernstein L,1988 : 48**:**246–253) , (Russo J, hasan Lareef M, balogh G, guo S, russo I,2003 : 1–25) .

Cortisol is an inducer of aromatase activity and treatment and a glucocorticoid inhibitor (RU486) results in a loss of aromatase activity that reflects cortisol involvement in this process. The promotion of breast cancer development with longer or higher cortisol in times of stress, therefore, occurs due to increased estrogen production. (Simpson E, ackerman G, smith M, mendelson C,1981: 5690–4) , (Schmidt M, loffler G,1997 : 197–204).

That is why the conversion of androgens to estrogen in stromal cells by the enzyme aromatase and its activity increases in stromal areas surrounding breast tissue and may promote the growth of breast cancer cells in vitro. (Simpson E,2003: 225–30) , (Brodie A, Lu Q, nakamura J,1997 : 281–6) .

Histone deacetylase inhibitor is a cancer treatment agent. The mechanism. (Bulun S, price T, aitken J, mahendroo M, simpson E,1993 : 1622–8) responsible for HDACI activation is unclear but the receptor 5 (DR5) causes cell death when it binds to TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) or agonistic anti-DR5 monoclonal antibody, and a combination of TRAIL / agonistic anti-DR5 anti-

DR5 monoclonal antibody and agents that increase DR5 exposure are expected as a new cancer treatment strategy. ATF3 stress response genes were needed for the effective use of DR5 by HDACI, and DR5 tests showed that ATF3 plays a key role in activating HDACIs in the DR5 gene expression. This provides important insights into how HDACIs show pro-apoptotic activity in anti-cancer treatment when used in combination with other treatment strategies. (Jia Liu, makoto Edagawa, hiroto Goshima, makoto Inoue, hideo Yagita, Zhonghu Liu ,ShigetakaKitajima et al ,2014: 320–6) .

An American cancer researcher found a direct proportion of high levels of stress due to aggression and was particularly affect black and Spanish women . (American Association for Cancer Research, Sept. 19, 2011. <http://www.aacr.org) , and Greek philosopher and physician Galen suggested that "melancholy" women are more likely to develop breast cancer and that if a person is psychologically affected, it affects the hormonal system that consequently depressed immune system. We can say that although psychological factors do not directly affect cancer, they do play a role in supporting it.(http://www.experts123.com/q/can-psychological-factors-cause-cancer.html)

Link between major life events with breast cancer and the relationship found between life events collection and increased risk of breast cancer in Poland such as divorce, death of husband, and death of a close relative or friend. (Joanna Kruk PhD, hassan Y.Aboul-Enein ,2004399-408), (Kirsi Lillberg ,pia K.Verkasalo ,jaakko Kaprio et al ,2003 : 415-23).

Objective:

Confirming statistical evidence on the relationship between psychiatric disorders and breast cancer confirms new allegations in management?

Patients and methods:

This is a case-control study that includes (620 patients) undergoing breast surgery for both benign and malignant lesions, from January 2009 to January 2020, average age (20-79) years (45.5) years; a total of six were men and the rest were women.

Patients were divided into two equal groups in both benign and malignant breast diseases. Those with malignant disease are considered a cases group while controlling one of those with benign one. Data collected from Al-Elwiya Maternity teaching Hospital, Al-Kindy Teaching Hospital and Private Clinics.

The study answered detailed questions including age, gender, psychological information (types, duration), histopathological type of breast cancer and immunohistochemistry of the three harmful receptors.

The 20-years interval is divided groups till age of

eighty years. The types of psychiatric disorders considered by patients diagnosed by psychiatrists and their sequence in their lives from baseline to the onset of malignancy in case group.

Mastectomy, local tumor excision or breast conserving surgery with axillary dissections performed for all those in case group. Types of mammary cancer documented in sheet of this

study from histo-pathological and immune-histo-chemical study of malignant specimens to evaluate the state of estrogen, progesterone and Erb_2 receptors in malignant specimens.

Results:

The study included (310) patients diagnosed with breast cancer classified as age group (20-79). Breast cancer was most common in the fourth and fifth decades of life as shown in Table (1).

Table 1: Number of patients with breast mass in both groups according to age groups.

ge	enign	Malignant
0-39	**116**	38
0-59	75	**129**
0-79	59	83

he chi-square statistic is 57.8569. The *p*-value is 0.00001.

Six (twenty-two in total) were men and two hundred and fifty were women who showed male genders and the risk of breast cancer less than (1%) compared to (80.6%) women in this study as shown in (table. 2).

Table 2: Number of patients with malignant breast mass according to gender.

ender	Benign	Malignant
ale	22	**6**
emale	250	250

The chi-square statistic is 8.666. The *p*-value is .003242.

Mental disorders in both patients groups were divided into acute, acute on chronic and chronic forms (77.40%) in the case group and (27.41%) in the control group as shown in (table.3).

Table 3. Types of psychological upset severity in both groups.

everity	enign	lalignant
cute	33	77
cute n ronic	27	103
hronic	25	60

he chi-square statistic is 3.2612. The *p*-value is .)5808. The result is *not* significant at < 05.

The duration in months of psychological upsets shown in (table .4)

Table 4: psychological upset duration in months in both groups.

uration	enign	Malignant
28	72	85
38	9	123
76	4	32

hi-square statistic is 61.3372. The *p*-value is < 0.00001

Where latent time of malignant mass appearance before Unescapable shock were (28, 38, and 76 months) respectively.

The Types of psychological diseases dominate in case group shown in (table.5)

Table 5: Types of psychological diseases in both groups.

Types	Benign	Malignant
Acute sever emotional reaction	65	26
Depression	1	35
PTSD	24	136
Anxiety	5	43

he chi-square statistic is 116.3443. The *p*-value is < 0.0000

Where acute sever psychological upset and (PTSD) might contribute to almost (67.5 %) of cases, anxiety with depressive disorder account for the other (36.25%).

Histo-pathological types of breast cancer become evident after surgery where invasive ductal cell carcinoma is the most common type as shown in (figure 1).
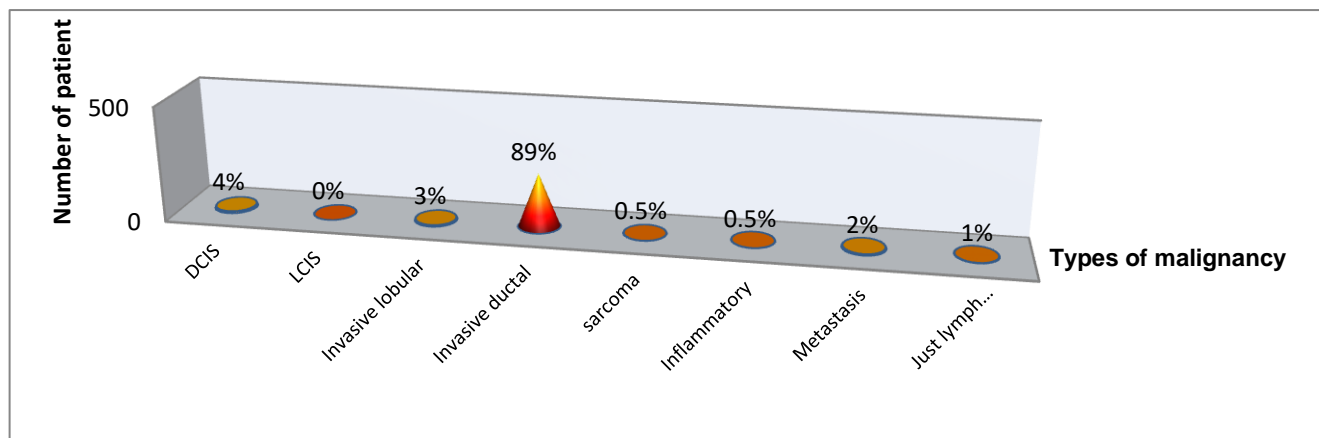
Figure 1: Percentage of patients according to types of malignancy.

Immune histo-chemistry are spectrum of results that carry importance in modulating strategy of treatment and clues for prognosis. Collecting or orphaned positive receptors rating almost (61.2 %) of cases while the analogous negative receptors cope with the rest (38.70 %). expression of HER2 receptors in almost (15 %) mostly premenopausal age group table (6).

Table 6: Immunohistochemistry receptors status.

nmunohistochemistry	Benign	nalignant
R,PR +VE	ot done	145
R,PR-VE	ot done	65
RIPLE -VE	ot done	55
ER2 +VE	ot done	45

he chi-square statistic is 116.3443. The *p*-value is < 0.

Discussion:

Prolonged exposure of breast tissue to sex hormones has a higher chance of developing genetic mutations with less potent remodeling as breast cancer is more prevalent over the years (table 1).

Being a woman is a higher risk of developing breast cancer, compared to low hormones and ineffective breast function in men. This describes the spread of the disease in the female gender (Table 2).

Psychological upset is not a substantiated risk factor for the cause of this disease with very few literatures concerning this aspect. By this research we have try to correlate these relations in preclinical, clinical and statistical trends; malignant lesions display significant relevance while benign one is not; as the former exhibit (77.40%) while the later demonstrate (27.41%) nexus with psychological disorders (tables 3). the non-significant p value might be due to patient inaccurate answer to questionnaire in consequence of socio-cultural reasons.

Acute and acute on chronic psychological upsets account for almost (75%) of positive cases and all were competent with time interval of each (table 4). These explain by the time were sectarian violence that happened in Iraq in 2006 which extend up to three years. [12] As the major life events and the timing of stress exposure has an effect on breast cancer risk, with early life stress exhibiting the association with breast cancer development. (Lilia Antonova , kristan Aronson, christopher R Mueller,2011: 208) , (Joanna Kruk, hassan Y. aboul-Enein,2004 : 399–40) **.**

high-intensity stress having a borderline link with the development of breast cancer; a conclusion evident from a meta-analytical study carried out with specific testing for an association between bereavement and breast cancer, and other life events (separation, war experiences, serious illness, financial problems, and work problems) and breast cancer. (Petticrew M, fraser J, regan M,1999: 1–17).

Furthermore, moderate and high daily stress showed a mild correlation with higher breast cancer risk in the West of Scotland Collaborative Study.(Metcalfe C, davey Smith G, macleod J, hart C,2007: 1060-5   Self-reported stress in the 5 years preceding the study baseline is associated with breast cancer risk.(Helgesson O, cabrera C, lapidus L, bengtsson C, lissner L,2003: 377-81).

The other (25%) from favorable circumstances provides a permanent form; chronic stress response and stress differentiates the immune response as a result of previous or similar stress experiences, depending on the type and severity of mental diseases, gender, or age. Both stress and depression are associated with a decrease in cytotoxic T-cells and natural-killer-cell activities that affect antibodies, as well as events that control the development and collection of somatic mutations and genomic instability. Better understanding of bidirectional interactions between neuroendocrine and antibodies influences new clinical and therapeutic strategies (Edna Maria Vissoci Reiche, sandra Odebrecht Vargas Nunes, helena Kaminami Morimoto,2004 : 617–25)

Various studies have suggested that changes observed in immunological activities among those with life-threatening episodes.(Schleifer SJ, keller SE, camerino M, et al,1983 : 374–7) . Other noted stress-induced disorders in neuroendocrine industries that may increase the production of various hormones, the findings of

which may explain changes in the hormonal environment. (Hilakivi-Clarke L, rowland J, clarke R, et al,1993: 141–60)

The opposing view states that the link between life events and the risk of breast cancer has been scientifically proven, but no studies have established a direct link between physiologic changes associated with these events and breast carcinogenesis . (Cohen S, herbert TB,1996: 113–42).

In this study the major emotional distress (PTSD) was (67.5%) while anxiety and depression (36.25%) showed a chronic form (table 5); these percentages may support a foundation that officially links all forms of resentment and cause or contribute to growth.(JOHN R. JACOBS and gregory B. bovasso ,2000 : 669-78) , (McKenna, molly C. et al,1999 : 520–31).

Concerning other aspect showed no discrepancy found with histo-pathological types after surgery; invasive ductal cell carcinoma is still the commonest variant of breast cancer representing (89%) of all cases (fig.1)

Utilizing genetic information assorts breast cancers into four groups for best treatment that include:

- Group 1 (luminal A). ER positive and PR positive, but negative for HER2 treated by hormonal therapy and may benefit from chemotherapy accounting (46.77%).
- Group 2 (luminal B). ER positive, PR negative and HER2 positive remedied by chemotherapy and may benefit from hormone therapy and treatment targeted to HER2.
- Group 3 (HER2 positive). ER negative and PR negative, but HER2 positive treated by

chemotherapy and treatment targeted to HER2; representing (14.51%).

- Group 4 (basal-like). Also called triple-negative, tumors that are ER negative, PR negative and HER2 negative. Are likely treated by chemotherapy which is (17.74%) (Table 6).

Over-expression of HER2 oncogene has been also shown to play an important role in the development and progression of certain aggressive types of breast cancer. Fortunately, small percent (14.51%) of our patients demonstrate this positivity.

Understanding all these steps and making it applicable in the management of breast cancer reduce both cost of treatment, comorbidity and mortality for both primary tumor and prevention of metastatic form by simple pharmaceutical agent like Beta blocker especially if path of metastasis via sympathetic system have proved with further studies and researches.

Enrolling psychological upset in the risk factors of breast cancer can modify types of treatment and expand spectrum of management ranging from commencement of event that need time from inescapable shock till appearance of primary lesion especially those women with other factors who are more vulnerable for breast cancer.

Further meta-analysis studies to prove psychological upsets as a risk factor may escalate treatments at different level of tumor growth with simple replacement of vitamins, immune modulating agent to biological therapy. This may extend to simple mastectomy with direct reconstructive measure in high-risk patients.

Encouraging outcome to decrease morbidity and mortality rates when combining with BRCA studies especially those patients with significant family history where prophylactic simple mastectomy with immediate reconstructive surgeries is achieved.

In conclusion Invention of this concoction proposed the need to inscribe psychological upset in list of breast cancer risk factors which consequently escalating management according to type of mechanisms and at any stage.

References:

1.Mansi Shah and Cinzia Allegrucci,(2012) **Keeping an open mind: highlights and controversies of breast cancer stem cell theory**, Breast Cancer, Dove Med Press, 2012; 4: 155-66

2. Nowell PC.(1976).**Clonal evolution of tumor cell populations**. Science. 1976; 194 (4260): 23–8. PubMed.

3. Spencer SL, Albeck JG, Burke JM, Sorger PK(2009). **Non-genetic source of cell-to-cell variation in apoptosis induced by trail**. Nature. 2009; 459 (7245): 428–32.

4. Marusyk A, Almendro V, Polyak K(2012). **Intra-tumor heterogeneity: a cancer-fighting glass?** Nat Rev Cancer. 2012; 12 (5): 323–34.

5. Chida y, hamer m(2008**) continual psychosocial elements and acute physiological responses** to laboratory-precipitated stress in wholesome populations: a quantitative assessment of 30 years of investigations. Psychol Bull. 2008 nov; 134(6):829-85.

6. Chrousos gp(2009) **pressure and disorders of the strain device**. Nat Rev Endocrinol. 2009 jul; five(7):374-81.

7.standish lj, sweet es , novak j, wenner ca, bridge c, nelson a, martzen m, torkelson c et al,(2008) ***breast most cancers and the immune system, magazine of the society integrative oncology.*** 2008; 6(four):158-68

8. Sravanth k Hindupur, Sai A balaji, Meera Saxena, Shubham Pandey1,Gopalkrishnashetty Sreenivasmurthy Sravan, Namrata Heda et al(2014**), identity of a singular AMPK-PEA15 axis within the anoikis-resistant increase of mammary cells,** Breast most cancers research 2014, 16 :420.

9. Nilsson mb, langley rr, fidler ij.(2005**) interleukin-6 secreted by using ovarian carcinoma cells of human**, is a potent proangiogenic cytokine. most cancers Res. 2005; (65): 10794-800.

10. WU S, Rodabaugh k, Martinez-mazao , Watson jm, Silberstein ds, Boyer cm, et al. (1992) ***stimulation of ovarian tumor cell proliferation with monocyte products including interleukin-1***, interleukin-6, and tumor necrosis element-alpha. American journal of obstetric & gynecology. 1992;166 :997-1007.

11. Ell ok, nishimoto R, mediansky L, mantell J, hamovitch .(1992) ***Social members of the family, social help and survival amongst sufferers with most cancers***. Journal of psychosomatic research. 1992 Sep;36(6):531-41. doi: 10.1016/0022-3999(92)90038-4.

12. Graham J, ramirez A, love S, richards M, burgess C.(2002**) traumatic existence stories and hazard of relapse of breast cancer**: observational cohort look at. BMJ. 2002 Jun 15; 324(7351): 1420. Doi: 10.1136/bmj.324.7351.1420

13. Algazi M, plu-Bureau G, flahault A, dondon MG, le MG.(2004). **Could remedies with β-blockers be related to a reduction in cancer threat?** Rev Epidemiol Sante Publique 2004;52::53–65. doi: 10.1023/B: CACO.0000036152.58271.5e.2004; 15:535–41.

14. Chris C. Wolford , stephen J. mc conoughey, swati P. Jalgaonkar , marino Leon, anand S. merchant et al(2013) ***Transcription factor ATF3 links host adaptive response to breast cancer metastasis,jour.of clini.investigation***, Volume 123, Issue 7, Pages 2754-3183.

15. Henderson B, ross R, bernstein L(1988): **estrogens as a cause of human cancer**: the Richard and Hinda Rosenthal Foundation award lecture. Cancer Res 1988, 48**:**246–253.

16. Russo J, hasan Lareef M, balogh G, guo S, russo I(2003)**. Estrogen and its metabolites are carcinogenic agents in human breast epithelial cells**. J Steroid Biochem Mol Biol 2003, 87**:**1–25.

17. Simpson E, ackerman G, smith M, mendelson C(1981). **Estrogen formation in stromal cells of adipose tissue of women**: induction by glucocorticosteroids. Proc Natl Acad Sci USA 1981, 78**:**5690–4.

18. Schmidt M, loffler G(1994)**. Induction of aromatase in stromal vascular cells from human breast adipose tissue depends on cortisol and growth factors**. FEBS Lett 1994, 341**:**177–81.

19. Schmidt M, loffler G(1997). **RU486 is a potent inhibitor of aromatase induction in human breast adipose tissue stromal cells**. J Steroid Biochem Mol Biol 1997, 60**:**197–204.

20. Simpson E(2003). **Sources of estrogen and their importance**. J Steroid Biochem Mol Biol 2003, 86**:**225–30.

21. Simpson E(2000). **Biology of aromatase in the mammary gland**. J Mammary Gland Biol Neoplasia 2000,5**:**251–8.

22. O'Neill JS, elton RA, miller WR(1988) **Aromatase activity in adipose tissue from breast quadrants**, a link with tumour site. Br Med J (Clin Res Ed) 1988, 296**:**741–3.

23. Bulun S, price T, aitken J, mahendroo M, simpson E(1993) *A link between breast cancer and local, estrogen biosynthesis suggested by quantification of breast adipose tissue aromatase cytochrome P450 transcripts using competitive polymerase chain reaction after reverse transcription.* J Clin Endocrinol Metab 1993, 77**:**1622–8.

24. Brodie A, Lu Q, nakamura J(1997) **Aromatase in the normal breast and breast cancer**. J Steroid Biochem Mol Biol 1997, 61**:**281–6.

25. Jia Liu, makoto Edagawa, hiroto Goshima, makoto Inoue, hideo Yagita, Zhonghu Liu' ,ShigetakaKitajima et al (2014) *Role of ATF3 in synergistic cancer cell killing by a combination of HDAC inhibitors and agonisticantiDR5 antibody through ER stress in human colon cancer cells, Biochemical and Biophysical Research Communications*,Volume 445, Issue 2, 7 March 2014, Pages 320–6 .

26. American Association for Cancer Research. "Association Found Between Stress and Breast Cancer Aggressiveness." Sept. 19, 2011. <http://www.aacr.org/home/public--media/aacr-in-the-news.aspx?

27. http://www.experts123.com/q/can-psychological-factors-cause-cancer.html.

28. Joanna Kruk PhD, hassan Y.Aboul-Enein (2004). **Psychological stress and the risk of breast cancer a case–control study**, Cancer Detection and Prevention . 02/2004; 28(6):399-408.

29.Kirsi Lillberg ,pia K.Verkasalo ,jaakko Kaprio et al (2003). *stressful Life Events and Risk of Breast Cancer in 10,808 Women: A Cohort Study*, Oxford Journals Medicine & Health American Journal of Epidemiology Volume 157,Issue 5 Pp.415-23.

30. Lilia Antonova , kristan Aronson, christopher R Mueller(2011)**. stress and breast cancer**: from epidemiology to molecular biology, Breast Cancer Res. 2011; 13(2): 208.

31. Joanna Kruk, hassan Y. aboul-Enein(2004) **Psychological stress and the risk of breast**

cancer: a case–control study**,** Cancer Detection and Prevention **,** 28, 6, 2004, 399–40.

32. Petticrew M, fraser J, regan M.(1999)**. Adverse life-events and risk of breast cancer**, a meta-analysis. Br J Health Psychol. 1999; 4:1–17.

33. Metcalfe C, davey Smith G, macleod J, hart C(2007) *The role of self-reported stress in the development of breast cancer and prostate cancer*, a prospective cohort study of employed males and females with 30 years of follow-up.;Eur J Cancer. 2007 Apr; 43(6):1060-5.

34. Helgesson O, cabrera C, lapidus L, bengtsson C, lissner L(2003). *Self-reported stress levels predict subsequent breast cancer in a cohort of Swedish women.Eur J Cancer Prev*, 2003 Oct; 12(5):377-81.

35.Edna Maria Vissoci Reiche', sandra Odebrecht Vargas Nunes, helena Kaminami Morimoto(2004) *Stress, depression, the immune system, and cancer, the lancet onc*ology, 5, 10, October 2004, 617–25

36. Schleifer SJ, keller SE, camerino M, et al(1983) *Suppression of lymphocyte stimulation following bereavement*; JAMA 1983;250:374–7.

37. Hilakivi-Clarke L, rowland J, clarke R, et al(1993) *Psychosocial factors in the development and progression of breast cancer. Breast Cancer Res Treat*, 1993; 29:141–60.

38. Cohen S, herbert TB(1996) **Health psychology**: psychological factors and physical disease from the perspective of human psychoneuroimmunology. Annu Rev Psychol1996; 47:113–42.

39. JOHN R. JACOBS and gregory B. bovasso (2000).*Early and chronic stress and their*

relation to breast cancer, Volume 30, Issue 3,May 2000 , pp. 669-78.

40. McKenna, molly C. et al(1999). *Psychosocial factors and the development of breast cancer: A meta-analysis*, Health Psychology*,* 18(5), 520–31.