

Pilot Study of Breast Cancer Patients with a Long Term Follow up in Erbil-Iraq

Suhel M Esmael Najjar (MB,ChB-DGS-MSc,PhD)¹

Abstract

Background: Breast cancer remains as the most common malignant neoplasm in females and one of the main life-threatening diseases, this long-term follow-up study under run for patients of carcinoma of the breast.

Objective: To gain practical feedbacks from the progression and fates of the patients who had been managed by the standard is previously known international guidelines.

Patients and Methods: This retrospective study involved (40) breast cancer cases In Erbil-Iraq for more than 15 years. Checkup tools were clinical examinations, laboratory investigations, and images for recurrence and metastasis. The following parameters had been studied; Age, clinical presentation, histopathological diagnosis, staging and management including surgeries, further adjuvant therapies and survival rates by periodic follow-up both in hospital and home visits.

Results: The results of this study showed that the left breast affected more frequently by 2:1 than the right. In 85% of patients, 1st presentations were in the 1-3 months and in stage II. Age's distribution was mainly between 31-60 years. Only 6 (15%) cases showed positive family history. The most common histopathology type was infiltrative ductal carcinoma 27(67.5%) and the prominent grades were (GII and GIII). Molecular based distribution of (Luminal B) was the biggest immunohistochemical type. About 70% of the cases were managed by quadrectomy or simple mastectomy and/or Axillary clearance. By (15) years follow-up (42.5%) cases lived between 5 to 10 years, and another (17.5%) survived above 10 years. No relation found between the cope of patients with her malignancy and course of the disease.

Conclusion: In the future, we have to concentrate on middle age and more scientific educations as they are most affected by (IDC) with advanced searching management routes. Older patient's carcinoma convention was less aggressive than younger, their life expectancy longer after diagnosis and treatment options. In the young group patient's tumor was more aggressive. Anyhow, breast cancer character remained unpredictable for various involved factors complexity and physiological variability of females. Recurrences, metastasis, and survival depend on familial and environmental code factors. Delay diagnosis is still a disaster in this locality that interferes with better results.

Keywords: Breast cancers, follow-up, management , prognosis

Corresponding Author: suhelnajjar6063@gmail.com

Received: 28th June 2020

Accepted: 21th July 2020

DOI:<https://doi.org/10.26505/DJM.19015450628>

¹ College of Medicine - Hawler Medical University - Consultant Surgeon Zheen and Rizgary Teaching Hospitals -Erbil- Iraq

Introduction

Breast cancer, which is considered to be the most prevalent female malignancy, and is the main cause of death in middle-aged women and its incidence is elevating[1]. Internationally breast cancer is the second most common cancer in the world and represents 9% of the global cancer burden. The malignant breast neoplasms are usually caused by their abnormal growth and uncontrolled proliferation of epithelial cells within the terminal duct and lobular parts of the breast[2]. Changes or mutations in DNA can cause normal breast cells to become cancer. Certain DNA changes are inherited and can greatly increase risks for breast cancer. Others are environmental causes that induce DNA mutation. But it's not yet known exactly how some of these risk factors cause normal cells to become cancer[1,2]. However, in patients with a suggestive personal and or family history, a specific predisposing gene is identified in <30% of cases[2]. Hormones seem to play a role in many cases of breast cancer, but just how this ensues is not fully understood but epidemiological and experimental evidence implicates estrogens in the etiology of breast cancer[3]. The cancerous cells can attack and destroy surrounding normal tissue, and spread throughout all parts of the body including the bones via bloodstream or lymph fluid to metastasize to new sites[4].

However, the metastasis time and site is still unpredictable and variable in various patients, newly found special mutated genes responsible for that [4,5] it has been proposed that breast cancer is a multifocal and multifactorial disease and its etiology is

interaction of the genetic and environmental factors[5]. Almost 90% of breast cancers occur sporadically, but without known predisposing genetic alterations, the remaining 10% are linked to genetic causes which include mutations in tumor suppressor genes, mostly BRCA1 and BRCA24. The incidence of breast cancer depends on the regions and countries, likely due to differences in racial and ethnic make-up, economy and social situations health resources, and lifestyle patterns[2].

With the introduction of molecular carcinoma cell subtyping the key of managements and prognosis is changed as the integration of morphological with molecular data has the potential to refine breast cancer classification, predict response to therapy, enhance understanding of breast cancer biology, and improve clinical management.

The early presentation, thorough approach and follow-up, experiences, team therapy and regarding all breast lumps malignant until proved otherwise moreover to ongoing researches and studies may restrict missing cases and entangles of diagnosis.

This study aimed to gain practical feedbacks from the progressions and fates of the patients who had been managed by standard international guidelines. To point out application deficiencies. To rearrange the next steps for more convenient future management.

Patients and Methods

In this revision (40) female breast cancer cases studied from May 2000 till December 2016 in which majority of them presented

with breast mass managed by a detailed history of first symptoms, duration, stature, full family history, marital status, pregnancies, contraceptive pills, economic conditions, behaviors, residency. Followed by non-invasive ultrasonography imaging then mammography with or without MRI, followed by FNAC cytology then standard malignant dependent surgical procedure performed according to their condition and after discussion by the management team of pathology, genetics, and oncology to the patient herself or and first-degree relative. The surgery took place in Rizgary teaching and Zheen international hospitals, by a team of two surgeons and anesthetics group, with the presence of histopathologists. Patients remained in the hospital for 3-5 days discharged home with further out-patient follow-up. The excised samples sent for laboratory for histopathological and immunohistochemical (ER, PR, Her2) studies were performed then the patients were referred to oncologist according to standard protocols and they were rechecked periodically during and after finishing adjuvant chemo and or hormonal therapy. The follow up was monthly first 6 months,

then every three months. Visitings after 12 months became every three months and then every six months. Follow-up also took place according to the patient's needs intermittently. Most visits were in the breast clinics and fewer in the patients' homes.

During follow-up clinical examination, CBC, Tumor markers CEA, CA15-3, CA27-29, annual CT scan for chest are performed.

Statistical analysis

Categorical and continuous variables were compared using (independent t-test) and identified standard deviation using Microsoft SSPS version 19 to measure P-value. When P-value was less than 0.05 regarded as significant, less as 0.01 highly significant, and above 0.05 regarded non- significant.

Results

From observed that early presentation of the patient is still not well established educationally as 20 cases (50%) presented beyond the first stage.

Table (1) showed that the major presenting symptom of breast cancer (BC) was a lump (80%) or localized mass rather than other symptoms.

Table (1): clinical presentation of patients

Type	Lump or localized mass	Nipple discharge	General breast mass	Ulcer with mass	Total
Number of cases	32	2	3	3	40
Percentages	80%	5%	7.5%	7.5%	100

The incidence of BC was more in the left breast than right observed by this Figure (1).

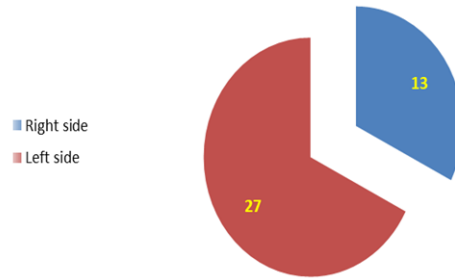


Figure (1): Left and right breast cancer incidences pie

Figure (2) likes most of other national and international studies the outer upper quadrant was predominantly affected by BC as the bulk of breast tissues lie their

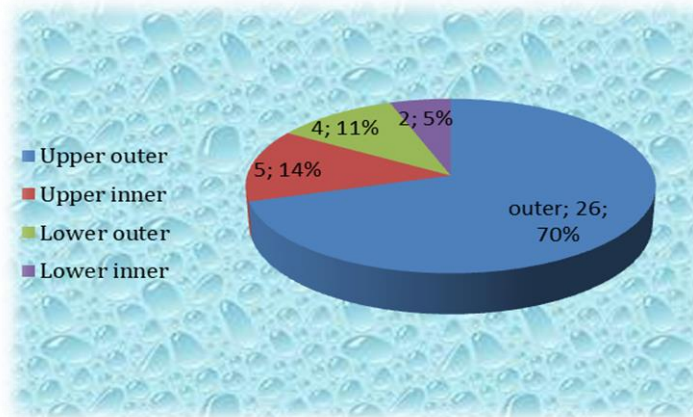


Figure (2): Demography of BC distribution in the breast

If we observe Table(2) we notice the late presentation of the patient predominant, as the patients searched clinical intervention after 1-3 months after appearing of their early symptoms and presented after their BC became prominent

Table (2): Duration of illness at time of presentation

Duration	≤1 month	1-3months	>3 months	total
Case numbers	14	16	10	40
percentage	35	40	25	100

Observing Figure (3), the middle columns (ages 41-60 years) showing a higher incidence of carcinoma of the breast this explains that the middle-aged are more prone to BC attacks like other nationalities. Anyhow the incidence increases more acutely above 50 years old.

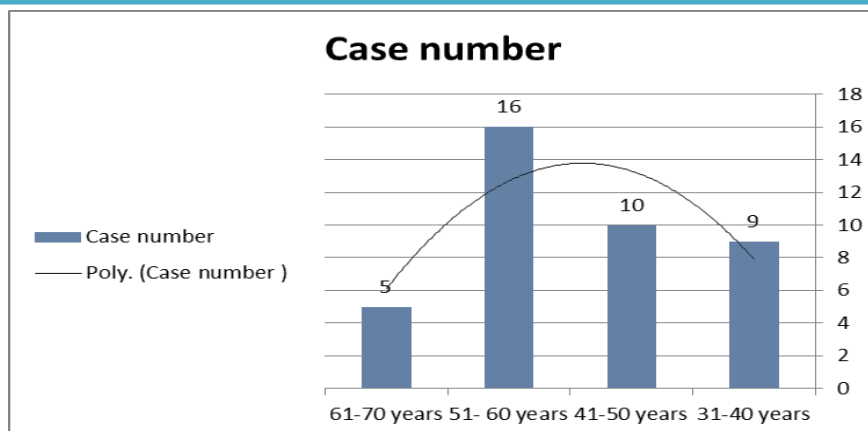


Figure (3): Peaks of age distribution of the cases

Regarding histopathological carcinoma, the most common type was invasive infiltrative ductal carcinoma (IDC) Table (3). Also, some other lobular carcinomas also observed.

Table (3): Histopathological classification

Pathology type	Ductal carcinoma in site (DCIS)	IDC		Inflammatory Carcinomatosa	Cystosarcoma phyllodes	Lobular carcinoma		Total
		INVs	N.INVs			Invs	N.Invs	
		20	7			5	2	
Numbers	3	27		2	1	7		40

The results of this study showed that most of the patients (ages up to 40) were presented in stage III followed by stage II, then stage I, regarding ages above 41 years greatest cases was in stage II that was 18 (45%) patients then followed by stage III which was 15 cases (37.5%) Figure (4). However sporadic cases attended in earlier or late stages.

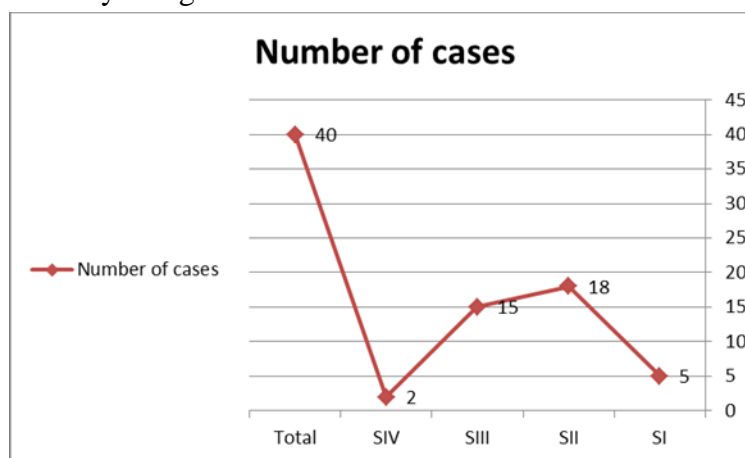


Figure (4): Presentation stages of the cases

From Figure (5), the cumulative advanced grading (poorly differentiated) type within this study was maximal and arranged between moderately to poorly differentiated, with late attendance of the patients lead to advanced stage presentations.

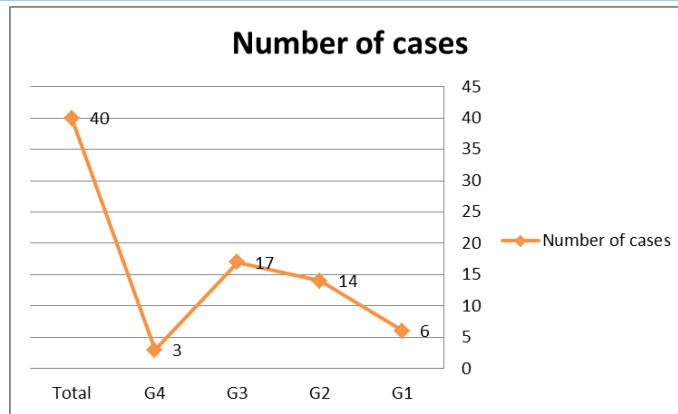


Figure (5): Grades of tumors

From Table (4) molecularly based sub-classifications of excised BC tissues were appointed to Luminal- B is predominant, or estrogen, progesterone positive, and Hert2 negative receptors. As the BC characterized

by heterogeneity and multi-locality; the Luminal-B indicates second generations of mother basal cell carcinoma, this also indicates more delay or obscured presentations.

Table (4): Immunohistochemistry stains

IHC stains	ER+	PR+	Her2+	Molecular basis
Negative	16	14	20	Triple negative/12
Positive	21	7	17	Luminal B/15
Strong positive	7	6	4	Luminal A/7

By observing Figure (6) About 6 cases (15%) showed positive family history, and religious distribution is nearly equal in comparison to

religious demographic distribution and no significant provoking effect is seen and P-value as it was more than 0.07.

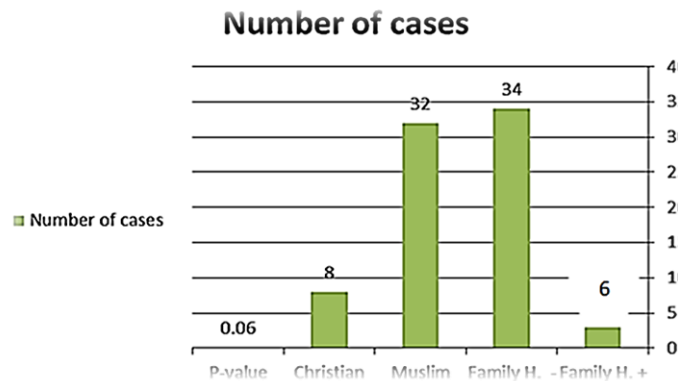


Figure (6): Family history & religion

Regarding the operation types used as seen in Table (5), most of the cases managed by quadrectomy or simple mastectomy and/or axillary clearance and according to indications and mainly due to size of the

mass and metastasis. No significant variability observed in the choosing of the type of operation as each operation mapped according to various interacting factors and rules of BC types.

Table (5): Type of operation

Operations	No surgery	Lumpectomy + axillary biopsy	1/4ectomy +axillary clearance	Simple mastectomy+ axillary dissect.	Modified radical mastectomy	P-value
Case numbers	2	7	11	17	3	0.07

From Table (6) below: only one case of chemotherapy. And another 2 cases used received did not receive adjuvant therapy, new adjuvant chemotherapy, and 26 (42.5%) and four cases received more than one course cases needed radiotherapy.

Table (6): Postoperative therapy

Therapy regimes	Hormonal		Radiotherapy		Chemotherapy	
	Yes	NO	Yes	No	More than one course	One course
Number of cases	32	8	26	14	6	34
Total	40		40		40	

Table (7) showed that 17 (42.5%) of the cases are survived for more than 5 years and (32.5%) of cases died before the continuation of 5 years survival. 7 (17%) patients more than 10 years and 13

Table (7): Survival duration

Years of survival	Not reached	<5 years	6-10 years	>10 year	Total	P-Value
Number of cases	3	13	17	7	40	0.046

Table (8) showed that coping of the patients and psychological response to the breast carcinoma diagnosis news not interfered with the pattern and progression of the BC as the P-value > 0.05.

Table 8: Patient's cope response to carcinoma

Response type	No.	Disturbed	Recurrence	Metastasis	Survival	P-Value
Good response	16	Not	4	6	15%	0.054
Bad response	24	Yes	2	6	46.3%	0.060

From Figure (7) a fungating, whole the breast involved inflammatory carcinomatosis BC which was managed by neoadjuvant chemotherapy and then operated on but unfortunately the patient died after one year.



Figure (7): A case of eroding left breast carcinoma

Discussion

For many years, there has been a widespread impression among clinicians that breast cancer in younger women is an aggressive disease, whereas among older women (≥ 60 years) the disease has a more indolent nature. This study has, to some extent, supported these ideas that all nine cases less than 30 years died within the first five years of follow-up. While tumors known to have an aggressive nature occur in all age groups, the increased incidence of grade III cancers among younger women does suggest a less favorable prognosis for this age group[6,7].

In this study the left breast more attacked by carcinoma, this phenomenon also mentioned by other studies as breast cancer is more common in the left breast than the right. The left breast is 5 - 10% more likely to develop cancer than the right breast, the cause till now is unknown[7,8].

The peak ages were affected included 41 to 61 years, this may fulfill mentioned international map of age distribution but lastly, some younger ages are also observed, putting in mind that last ten years included

these young ages which correlate the wear and tear stress of the area conditions as blamed to be cause for breast cancer although studies result for stress effects on carcinoma of breast are non-conclusive[7,10]. While (Yujing J Heng et al 2017) as a Japanese study cited that young ages are frequently affected but we found nearly young and olds are affected evenly and non-significantly older ages more same idea confirmed by (Deng C. X -2006)[9,11].

The majority of cases in this study were stage 2(48%), stage 3(43%) and then stage 1(9%). Such findings have also been documented in some Arabic countries, while in developed countries; most patients may present with early stages and may be ticked during ordinary breast screening[9,10,11].

The delays as also mentioned by (E.Donald et al 2003) are mainly due to the lack of perfect health education, delay medical consultation, absence of perfect health system of screening, rejection of management strategy, and defects in a follow-up. This result was also in agreement with a study in Iran which concluded that stage II is the most prevalent followed by

stage III did by Mosavoui[14]. A young patient attended in stage- 4 the husband blamed the unavailability of a female doctor in this specialty (religious Custom). Anyhow this is regarded as one of the causes of delayed presentation [14,15].

Molecular based classification this studies triple-negative model predominance in the cases are analogous with the internationally mentioned heterogeneity of breast cancer cases, and showed GIII nature tumor cells[14,15,16]. We found a strong correlation between female residency and environmental influences on breast carcinoma but special studies in this regard either missing or controversial[18,19]. The recurrences were as usually mentioned by various references included: cases of pulmonary invasions, cases of liver metastasis, a case of thoracolumbar vertebral invasion, and two cases of brain metastasis by these metastases we observed correctness of idea proposed that breast cancer is intrinsically a systemic disease. New molecular technologies, such as DNA microarrays, support the idea that metastatic capacity might be an inherent feature of breast tumors[19,20].

Observable unpredictability of breast carcinoma with a variable period of time developed metastasis and died. This may indicate that the metastasis is a basic carcinoma genetic map dependent more than the environmental severity of toxication [21,22,24]. As we observed from basic molecular classification the triple-negative cases were predominant which indicates heterogeneity and aggressiveness of the tumor's cellular character and by grading

distribution were grad-3 these are normal to each personal and carcinoma cell character moreover to early diagnosis[18,21,23].

Conclusions

In this study, we concluded the following:

1. In this country, breast cancer was diagnosed in late-stage due to a lack of education of females.
2. If patients were treated properly even in the second stage the prognosis is amnestic and aggressive surgical operations were not essential.
3. Although genetic factors are blamed in all researches as 10% of causes of carcinoma of breasts, but in this study, well-observed environmental and stress factors are encountered more and blamed.
4. No relation and course changes observed by type of patients coping with carcinoma of the breast.

Recommendations

Management methods till now are only symptomatic and palliative, an original mother cell carcinoma genetic reformatting is the only radical treatment which is optimized and required. Accordingly most of our future studies should concentrate on genetic researches and team working.

References

- [1] Parkin D. M. and Coleman M. P., "Changes in diet and changes in cancer risk", Observational studies. IARC Sci Publ, PP. 93-111. (1990).
- [2] S. Shiovitz and L. A. Korde. Genetics of breast cancer: a topic in evolution. Ann Oncol. 2015 Jul; 26(7): 1291–1299. Published online 2015 Jan 20. doi: 10.1093/annonc/mdv022.PMCID: PMC4478970 .PMID: 25605744.

- [3]Ruth C Travis,corresponding author and Timothy J Key. Oestrogen exposure and breast cancer risk. *Breast Cancer Res.* 2003; 5(5): 239–247. Published online 2003 Jul 28. doi: 10.1186/bcr628. PMID: 12927034.
- [4]Ricardo Romero-Moreno, Kimberly J. Curtis, Thomas R. Coughlin, Maria Cristina Miranda-Vergara, Shourik Dutta, Aishwarya Natarajan, Beth A. Facchine, Kristen M. Jackson and et al. The CXCL5/CXCR2 axis is sufficient to promote breast cancer colonization during bone metastasis. *Medical press. Open Access.* Published: 27 September 2019 DOI: 10.1038/s41467-019-12108-6.
- [5]Danny R Welch,corresponding author, Patricia S Steeg, and Carrie W Rinker-Schaeffer. Molecular biology of breast cancer metastasis: Genetic regulation of human breast carcinoma metastasis. *Breast Cancer Res.* 2000; 2(6): 408–416. Published online 2000 Jul 21. doi: 10.1186/bcr87 PMID: 11250734.
- [6]Parkin D. M., Bray F., Ferlay J. and Pisani P., "Estimating the world cancer burden", *Globocan. Int. J. Cancer*, 94, pp. 153-156. (2001).
- [7]R Taramelli, F Acquati. The human genome project and the discovery of genetic determinants of cancer susceptibility. *Eur J Cancer* 2004 Nov;40(17):2537-43. doi: 10.1016/j.ejca.2004.07.030.PMID: 15541956
- [8]Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. (January 2016). "American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline". *Ca.* 66 (1): 43–73. doi:10.3322/caac.21319. PMID 26641959.
- [9]Yujing J Heng , Susan C Lester, Gary Mk Tse, Rachel E Factor, Kimberly H Allison , Laura C Collins "et al". The Molecular Basis of Breast Cancer Pathological Phenotypes. *J Pathol .* 2017 Feb;241(3):375-391. doi: 10.1002/path.4847. Epub 2016 Dec 29. PMID: 27861902 PMID: PMC5499709 DOI: 10.1002/path.4847.
- [10]Deng C. X., "BRCA1: cell cycle checkpoint, genetic instability, DNA damage response and cancer evolution", *Nucl. Acids Res*, 34(5), pp.1416-1426. (2006).
- [11]Nagi S El Saghir 1 , Mazen K Khalil, Toufic Eid, Abdul Rahman El Kinge, Maya Charafeddine, Fady Geara, Muhieddine Seoud, Ali I Shamseddine. Trends in Epidemiology and Management of Breast Cancer in Developing Arab Countries: *Int J Surg* 2007 Aug;5(4):225-33. doi: 10.1016/j.ijsu.2006.06.015. Epub 2006 Aug 24. PMID: 17660128.
- [12]McPherson K., Steel C. M. and Dixon J. M., "Breast cancer epidemiology", risk factors and genetics. *Br. Med. J.*, 321, pp. 624-628. (2000).
- [13]Britta Weigelt. Breast cancer metastasis: markers and models. *Nat Rev Cancer.* 2005 Aug;5(8):591-602. doi: 10.1038/nrc1670.7- PMID: 16056258 DOI: 10.1038/nrc1670.
- [14]E.Donald, E. H., Kenneth, C. C., Paul, H. L., "Histologic Grade, Stage, and Survival in Breast Carcinoma", *Cancer*, Vol. 98, No. 5, pp. 908-917. (2003).
- [15]Yu-Ting WuShou-Tung ChenChih-Jung Chen. Breast cancer arising within fibroadenoma: Collective analysis of case reports in the literature and hints on treatment policy. November 2014 *World Journal of*

- Surgical Oncology 12(1):335 DOI: 10.1186/1477-7819-12-335.
- [16] Mousavi, S. M., Montazeri, A., Mohagheghi, M. A., Jarrahi, A. M., Harirchi, I., "Breast cancer in Ira: An epidemiological review". The Breast Journal, Vol. 13, No. 4, pp. 383-391. (2007).
- [17] Saadat, Sabiha. "Can We Prevent Breast Cancer?". Print. Int J Health Sci (Qassim). 2008 Jul; 2(2): 167-170. PMID: PMC3068727- PMID: 21475500.
- [18] Joseph A Shehadi , Daniel M Sciubba, Ian Suk, Dima Suki, Marcos V C Maldaun, Ian E McCutcheon, Remi Nader, Richard Theriault, Laurence D Rhines, Ziya L Gokaslan . Cancer Metastatic to the Spine: A Review of 87 Patients.. Eur Spine J 2007 Aug;16(8):1179-92. doi: 10.1007/s00586-007-0357-3. Epub 2007 Apr 4. PMID: 17406908 PMID: PMC2200772- DOI: 10.1007/s00586-007-0357-3.
- [19] Mohammed Al-Azri MD, MRCGP (INT), MMedSc, PhD Huda Al-Awisi BSc (HONS), MSc Mansour Al-Moundhri BSc, MRCPUK, FRACP, MD. Coping With a Diagnosis of Breast Cancer-Literature Review and Implications for Developing Countries. 02 November 2009 <https://doi.org/10.1111/j.1524-4741.2009.00812.x>Citations: 51.
- [20] Kornelia Polyak, " Heterogeneity in breast cancer" J Clin Invest. 2011 Oct 3; 121(10): 3786-3788.
- [21] Abeer, A. Al-Mowali, Sawsan, S. Al-Haroon and Saad, A Abdualah., "Study of BRCA1 and BRCA2 Gene Mutations in Relation to Clinico-pathological Criteria of Breast Cancer in Basrah", Research Journal of Pharmaceutical, Biological and Chemical Sciences, Vol. 5, No. 5, pp. 1217-1222 (2014).
- [22] Minouk J. etal (Psychological stress, adverse life events and breast cancer incidence: a cohort investigation in 106,000 women in the United Kingdom): Breast Cancer Research 2016 18:72.
- [23] NicoliniabR.GiardinobA.CarpicP.Ferrari aL.AnselmiaS.ColosimodM.ConteeM.FinibG .GiavaresibP.BertieP.Miccolie. Metastatic breast cancer: an updating. Elsevier- Volume 60, Issue 9, November 2006, Pages 548-556. <https://doi.org/10.1016/j.biopha.2006.07.086>.
- [24] Beatriz Martins Tavares Murta, Jother Soares Machado, Mateus Zaparoli, Vítor Carvalho Lara. Eddie Fernando Candido Murta. The relationship of host immune cells, cytokine and nitric oxide production to tumor cells in ovarian carcinoma. Sao Paulo Med. J. vol.117 n.2 São Paulo Mar. 1999. <https://doi.org/10.1590/S1516-31801999000200008>.