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REVIEW: BREAST CANCER IN SAUDI ARABIA: MOLECULAR GENETICS AS INITIAL DIAGNOSIS

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ABSTRACT

The breast cancer is mainly common cancer in Saudi Arabia. Moreover, is estimated that in near future the incidence will increase and mortality rate will reach 160%. Therefore, this review to contribute in the early detection of breast cancer among using sophisticated techniques. In conclusion, gene mutations regarding breast cancer are promising field in Saudi Arabia. Although there are several studies done, but still epidemiological complementary and comprehensive study is desirable to concentrate on the gene mutations that found significantly positive in Saudi community. Particularly, some studies done confirmed that Saudi women were very interesting in testing breast cancer genetically to avoid the late stage of the disease and early detection of the disease may lead to good prognosis.

KEY WORDS: Saudi Arabia, Breast Cancer, Molecular Genetics, Gene, Mutation.

INTRODUCTION

Breast cancer is an extremely public malignancy, affecting one in eight women during their lifetime. In both developing and developed countries breast cancer is performing as common health problem. In Arab countries, breast cancer is the main frequently diagnosed malignant disease in females.[1] The breast cancer incidence in Arab countries is lower and rising fast than in Europe and the USA.[1] Breast cancer is a most important cause of female mortality, with more than 458,000 deaths estimated worldwide in 2008.[2-3]

Data of breast cancer from Arab countries was varying according to the region and country. Several countries of Arab have observed huge urban development and spread industrialization. The majority of the people in Arab countries reserved away from enjoying

the medical discovers of the second part of the twentieth century due to armed struggles, political unpredictability, and poor system. Investment in investigation and research has insulated and stay behind as matter of individual and institutional incentive.[4] Highly developed disease remains very popular in Egypt, Tunisia, Saudi Arabia, Syria, Palestinians and others.[4-5]

The most common cancer among Saudi females is breast cancer, about more than 24% of all newly diagnosed cancer cases reported are breast cancer.[6-7] Breast cancer is considered as the most implacable malignancy and the most important reason of death in Saudi Arabia.[8-9] There were 1473 cases of female breast cancer in year 2010. In year 2010 breast cancer graded as first cancer accounting among females, about 27.4% out of (5,378) cancers cases of all newly diagnosed female cancers.[10] Moreover, it is estimated that by year 2025, the incidence will reach to 350% and mortality of 160%.[6,8, 11-12] Moreover, carcinoma of the breast that developed before the age of 40 was significantly more common in Saudi women compared with patients in the USA.[13 -14]

In different specialized centers, early breast cancer is rising and still large numbers of women come with metastatic breast cancer in most Arab countries. [4] The reasons for this situation included shyness, apprehension of cancer, difficult admission to health care facilities, and destitute health education.[4]

Therefore, the aim in Arab countries should be decreased the incidence of great tumors and appearance of late stage of disease. The implementation of universal guiding principle has to be modified to local situations, and programs of breast cancer should have aim of early stages diagnosis.[15]

Information of the descriptive epidemiology of breast cancer is valuable both in suggesting of hypotheses of etiology and identified of preventive measures in define groups at high-risk to be targeted for preventive efforts.[16-17]

Breast tumors are well known as highly heterogeneous tumors with diverse biological, pathological, clinical characteristics and response to treatment which has been attributed partially to various risk factors including reproductive, genetic and environmental.[18-20] Many recent reports have restated its heterogeneity based on molecular and genetic profile and classification.[20-22] Breast cancer is not a solitary unit but a diverse group of bodies. Progress

in gene profiling appearance and immunohistochemistry have led to exposure of new molecular subtypes of breast cancer, resulting in the crisis of a more complicated classification systems that are therapeutically and prognostically more analytical.[8]

Treatment and prevention procedures are progressively more particularly the molecular classification that has been established during the last 10 years.[23-25]

The current review provides knowledge on molecular basis of early diagnosis in breast cancer patients in Saudi Arabia which enhancement the detection of breast cancer and this may lead to upright prognosis.

Epidemiology

Cancer control has become an objective of global health, as increasing rates of noninfectious diseases in low-resource settings have appropriately propelled it into the attention. Inclusive plan for cancer control are required to efficiently manage the disease burden. [26] In Arab countries, the most frequent cancer in women is breast cancer which occurs in young women of around 50 years.[4-5, 8, 27-29]

Breast cancer is considered as common malignancy and represents after the lung cancer as second leading cause of cancer deaths. That malignancy conveys fabulous socio-economic, emotional and public health effects.[8, 30] The breast cancer incidence in Saudi Arabia was 19.8% of all the female cancers detected in the Kingdom.[9, 31-33]

Saudi National Cancer Registry accounting an increasing quantity of breast cancer among women of different ages from 10.2% in 2000 to 24.3% in 2005 to 27.4% in 2010.[8, 34- 37]

In 2010, about 1473 cases of breast cancer in Saudi women. Breast cancer reported in 27.4% of females of all newly cases diagnosed (5,378) in female in year 2010. For female population the ASR was 24.9 per 100,000. The regions with the highest ASR were Eastern region at 39.5 per 100,000, Qassim region at 32.8 per 100,000, Riyadh Region at 30.6 per 100,000, Makkah Region at 24.2 per 100,000 and Madinah Region at 21.3 per 100,000. The median age at diagnosis was 49 years at range between 21 and 120 years.[10]

Breast cancer was the majority common tumor among the females followed by the cancers of thyroid, Colo-rectal, NHL, Corpus Uteri, Leukemia, Ovary, Liver, Skin, and Hodgkin Disease.[10] Table-1.

In spite of the minor crude incidence rate of breast cancer in woman in Saudi Arabia when compared with other communities in developed World, the Saudi Cancer Registry accounted that breast cancer was the most frequent cancer among woman during a 14-year period (1994–2008) in Saudi Arabia.[38] While in the study done between 2001-2010 at King Khalid University Hospital using breast tissue specimens, they found 35.8% were malignant cases in women.[34] Alghamdi et al.,[38] stated that the breast cancer is an important health problem in Saudi Arabia and considered breast cancer to be one of the most common causes of death.

Table -1: The Most Common Cancers in women in Saudi Arabia (2010) per 100,000 women [10]

The region	Type of Cancer										
	Breast Cancer	Thyroid	Colo-rectal	NHL	Corpus Uteri	Leukemia	Ovary	Liver	Skin	Hodgkin Disease	Other Sites
Riyadh	25.5	11.5	9.6	5.6	3.5	5.2	2.6	3.8	3.0	3.0	24.3
Makkah	29.9	9.1	10.6	6.7	4.7	4.5	2.7	2.5	-	2.2	24.5
Eastern	33.9	10.9	7.8	4.3	4.1	4.3	3.3	-	2.2	2.7	24
Madinah	25.8	10.0	8.8	4.2	3.9	5.5	3.9	-	3.0	3.9	23.6
Northern	28.3	7.5	5.7	-	3.8	5.7	-	-	3.8	-	26.4
Qassim	34.2	10.6	10.3	5.0	3.3	3.3	2.3	-	3.0	3.0	21.9
Jazan	18.8	3.7	7.3	5.2	-	-	7.3	2.6	8.4	-	26.7
Hail	25.2	11.7	8.7	5.8	4.9	2.9	3.9	4.9	-	-	23.3
Najran	17.6	13.5	8.1	6.8	5.4	4.1	-	2.7	2.7	2.7	12.2
Baha	25.0	9.8	8.7	5.4	9.8	-	4.3		4.3	-	22.8
Asir	17.9	7.3	9.1	7.5	6.0	5.7	4.7	3.4	3.1	-	32.2
Tabuk	17.5	8.8	10.2	5.1	2.9	5.8	2.9	7.3	3.6	5.1	19.7
Jouf	20.9	20.9	4.4	3.3	3.3	9.9	3.3	-	-	-	19.8

The Risk Factors

Amount of risk factors of breast cancer have been known for many decades, particularly those related to reproductive exposures and hormonal.[39-40]

Ageing is one of the single utmost risk factors for the new breast cancer development.[41-42] According to Saudi National Cancer Registry report an increasing of breast cancer proportion among women of different ages from about 10.2% in 2000 to 24.3% in 2005[43] to 27.4% in 2010.[10] The highest rate of breast cancer was recorded in age group of 30-44 years and lowest rate was in women over 75 years.[10] Table-2 In young patients, breast cancer is frequently related with low quality prognosis and young age; less than 40 years is a risk factor for decline breast cancer in Saudi patients.[13]

The breast cancer incidence in Saudi Arabia was low comparing with other Gulf Cooperation Council countries,[17] most of the cases of breast cancer in females were found in Qassim Region at 34.2 per 100,000 women followed by Eastern Region 33.9, and Makkah Region 29.9.[10] Table-1 while the lowest cases noticed in Tabuk Region at 17.5 per 100,000 women, Najran 17.6, and Asir 17.9. [10] El Hag et al., [44] noted the regional variations in Saudi Arabia. According to the report of Saudi cancer published in 2007 recorded higher incidence in Makkah region then Riyadh, Tabuk and Qassim regions while Jazan and Asir regions the incidence rates was lowest. [45] In other study consist of all cases of breast cancer in Saudi women which started from 2001 to 2008 and done by Alghamdi and his team[38] they studied the age-standardized incidence rate (ASIR) and the crude incidence rate (CIR), adjusted by the region and year of diagnosis and they found that the Eastern region of Saudi Arabia had the highest total of ASIR, about 26.6 per 100,000 women, then Riyadh 20.5 then Makkah at 19.4 while Jazan, Baha, and Asir had the lowest average of ASIRs, at 4.8, 6.1, and 7.3 per 100,000 women, respectively. The region of Jouf (24.2%; CIR 11.2, ASIR 17.2) had the highest adjusts in CIR and ASIR from 2001 to 2008. But Qassim, Jazan, and Tabuk reported lowest rates with negative values.[38]

The relationship between breast cancer and pregnancy was studied in Saudi Arabia in two studies, the first one done in Riyadh where 28 women investigated with diagnosis of

breast cancer during pregnancy. The results showed no significant difference in overall survival and relapse-free survival as compared with age and stage matched controls. Chemotherapy after the first trimester of pregnancy carried no significant morbidity. The studied concluded that pregnancy does not appear to be an adverse prognostic factor for breast cancer.[8, 46] The second study also done in Riyadh, they reviewed the medical records of 220 patients to study the incidence of breast cancer during pregnancy and concluded that pregnancy may not be considered as an etiological factor for breast cancer.[47]

The association between breast cancer and breast feeding was studied in Saudi Arabia during 80s. The study suggests that the incidence of breast cancer was low during 80s among Saudi women. The results showed that breast feeding do not give any protection to the patients.[8, 48]

In study done in Dammam they found menopausal status had no significant influence on survival in a low risk population.[8, 49]

A case-control study was conducted on 499 women with breast cancer attending an Epidemiology and Scientific Computing Nutrition Researching Riyadh during 1996-2002. Serum levels of total cholesterol and triglycerides were measured in previous study. The results showed a significant association between intake of fats, protein, and calories and risk of breast cancer.[8, 50]

The relationship among diabetes as risk factor increase the possibility of causing breast cancer done in Hail, they found that diabetic female patients at a younger age in population are susceptible to developing breast cancer.[51] Another study done in Riyadh in obese and diabetic premenopausal patients and found that effect on adipocytokines and inflammatory mediators contribute to increase breast cancer risk in premenopausal women.[8, 52]

Table-2: Incidence of Breast Cancer in Women among Age Group [10]

Age group	Incidence
All Ages	27.4
0-14 Years	0.0
15-29 Years	25.2
30-44 Years	41.2
45-59 Years	36.1
60-74 Years	21.3
> 75 Years	13.2

Also, some case control study done in Riyadh, they found that about 74.7% of women suffer from pre-menopausal were either obese or overweight while premenopausal controls was only 58.5% of revealed BMI ≥30 with (OR =2.47, p <0.0001), representing two-half double raised in risk of breast cancer among obese patients with premenopausal. In the females with post-menopausal, obese female has 66% increase chance of breast cancer compared to lean post-menopause.[53]

Study was done on estrogen alterations and receptors of progesterone and Her-2/neu oncogene protein expression in breast ductal carcinomas. The results substantiated the point that development of breast cancer is associated with modifications of ER, PgR and HER-2/neu expression in 100 mastectomy specimens from Assir, Abha.[8]

In Saudi Arabia due to religion believe alcohol is not available and therefore its consumption is not one of the risk factor for those populations. Similarly, smoking cigarette was not an ordinary performed among females in Arab countries. Certainly, only 29.8% of cases and 28.8% of controls ever smoked. Nevertheless, this difference was not significant, suggesting that no association between cigarette smoking and breast cancer in this population.[53]

In case control study done, the linked between breast cancer and obesity was investigated in Arab populations, there was strong significant between controls and patients according to their BMI. The ratio of overweight/obese (BMI ≥25) in females was significantly higher among patients with breast cancer (75.8%) comparing with healthy controls (61.3%) (OR =1.74 and p <0.0001). The result confirmed that obesity is one of the risk factor for breast cancer in women in Arab populations. [53]

Socio-demographic Factors

To enhance knowledge of the decision makers about cancer genetic counseling or testing, it has become progressively more important to increase a better considerate of cultural, admission, and psychosocial background correlated to factors manipulate the health services used.[6,54-55] The low use of genetic testing in the Arab American population is likely due to structural and cultural barriers that reduce access to preventative healthcare. Applicable structural fences to breast cancer screening include a lower level of income.[56] Cultural barriers to screening include the fear and shame associated with cancer, defeatist religious beliefs, misapprehensions about genetic inheritance, worries of being typecast by healthcare providers, and concerns about diffidence, which might prevent women from discussing sensitive topics such as breast health or undergoing examination by male physicians. [57- 60]

In Saudi Arabia, the awareness regarding breast cancer genes, the interest in breast cancer genetic testing and factors that may influence this interest is lacking despite the expected wide spread implementation of these tests in the clinical perform. Subsequently, it is essential to understand the factors that associate to interest and utilization of cancer genetic services.[6]

In Al Hassa Governorate Eastern Province of Saudi Arabia, a cross-sectional survey study was done, by Amin et al[6] regarding the socio demographic factors in Saudi women according to their interest in breast cancer gene testing. They concluded that 11.2% were illiterates, 76 (12.7%) had primary/preparatory level of education. Most of them were occupying governmental jobs. Out of 599 participants, 122 (20.4%) of them had a positive family history of breast cancer among ≥3 relatives before the age of 50 Family members of immediate family were mentioned to be affected in 26.2% (mothers n=14, sisters n= 12, brother n=1, grandmother n=7). Most of women participated in this survey had monthly income between 5000 to 10000 Saudi Riyals and the study showed almost two thirds of the participants had demonstrated favorable attitude towards breast cancer genetic testing and they concluded that Saudi women expressing great interest in testing risk for breast cancer genetically despite their poor awareness.[6]

Another control study done in Saudi women at King Faisal Specialist Hospital & Research Center (KFSH&RC) in the Oncology Department Riyadh, this study associated between breast cancer and obesity.[53] A bout 1172 women were included, 22.9% of the women participated were illiterate, aged ≤35 years, 89.5% married, 43.6% working, and 38.1% were obese. Socio demographic risk factors of breast cancer were studied which included the history of breast cancer in the family; education and occupation, the marital status were investigated in patients with breast cancer comparing with healthy controls. Interestingly, high significance was found between the history of breast cancer in the family and new cases of breast cancer higher proportion of cases (21.9%) when comparing with controls (11.4%).[53]

Diagnosis

Perfect and suitable breast cancer diagnosis is a significant and regularly disregarded aspect of breast cancer management. Two important facets are included: (a) confirmation of diagnosis of cancer based on clinical assessment and sampling of tissue, and (b) imaging testing with tumor markers desirable for treatment scheduling.[53]

Breast imaging diagnostic valuation; needed needle sampling of doubtful lesions, and informs level of disease. In low-resource settings, ultrasound is widespread technology, a low cost, that can be a particularly valuable addition to CBE giving details regarding the size and degree of thickenings and masses.[61]

Perfect histopathologic or cytologic diagnoses are wanted before starting the treatment. Quality surgical pathology is significant to perfectly differentiate between benign opposed to malignant and persistent versus noninvasive disease. Sampling of tissue techniques differ by resource level and reveal growing factors in cytology and pathology proficiency. Needle biopsy is choice to surgical removal for preliminary diagnosis of most breast lesions doubtful, unless resource limitations stop this, in which case surgical removal is necessary. The function of aspiration of fine-needle opposed to core needle biopsy continues to be argued, and may differ depending on requirements and local conditions.[62]

Screening mammography starting from beginning of 1980s led to sweeping enhancements in early cancer detection.[26, 63] Mammography has been shown to be the most effective method of finding small Breast Cancer and presumably will give a patient the best opportunity for cure or at least long–term survival.[11-64]

Screening mammography normally is recommended for women over the age of 50 years; however, many authorities also recommended that be ongoing at age 40.[65]

Self-examination of the breast is a simple, low cost, noninvasive adjuvant screening technique for the discovery of quick breast cancer in women.[66] Its reason is 2 fold: to create women acquainted with both the occurrence and the touch of their breasts and to help women notice any changes in their breasts as quick as possible. There is indication that women who properly practice BSE monthly are more likely to notice a swelling in the early phase of its development, and early diagnosis has been stated to effect early treatment and to produce a better survival rate.[67]

Molecular Genetic

The first gene related with domestic breast cancer tendency called Breast Cancer Associated gene, *BRCA1*, which was known in 1994.[68-69] Since then, the hereditary breast cancer, have been found to be associated with about 5- 10% of all mutations of *BRCA1* of breast cancers. Women having germline mutations of *BRCA1* are more probable to progress violent tumor of breast at an early age (<50).[70-71] *BRCA1* promoter methylation has been noticed in DNA from both tumor tissues and WBCs in three out of seven breast cancer patients from breast ovarian cancer families.[72-73] This suggested that *BRCA1* promoter methylation happening in normal tissue of the body is connected with the progress of *BRCA1*-like breast cancer.[72-75]

The *BRCA1* missense mutations associated with disease is located in the N-terminal RING or C-terminal BRCT domains, suggesting that these regions are critical for the tumor suppressor activity of the protein.[76-79]

Genetic testing for predisposition to malignancy seems to be particularly useful in families where high risk of cancer is known. In these families, testing for the molecular

lesions in the 2 genes is favoured as it generates useful information for genetic counseling and it bears potential diagnostic value and potential clinical benefits.[80]

A mutation in either *BRCA1* or *BRCA2* awards an improved risk of breast and other cancers. Great reorganizations and deletions in *BRCA1* or *BRCA2* can also vary the purpose of *BRCA*, resulting in the same clinical syndrome to that seen in carriers of mutations in these genes.[81-82]

Many studies were done regarding the prevalence of gene mutations in breast cancer patients in Saudi Arabia. The more recent one done by Nemenqani et al[83] the researchers observed significant relations between *ER* status and the *FOK1* polymorphism. Their results demonstrated that *f* allele and *FOK1* genotype have significant function in breast cancer risk in Saudi patients. They concluded that an increased risk of breast cancer among women with the *ff* genotype. This relationship seems to be modified by estrogen receptor status of the tumor. These findings suggested that the vitamin D pathway is a potentially important mediator of breast cancer risk. The VDR may represent an important target for breast cancer prevention.[83] Related study concluded the occurrence of a strong relation between abnormal methylation of the *BRCA1* promoter in WBC and breast cancer –related molecular changes, which designated the likely propensity of the carriers for progressing breast cancer. This notifies the potential use of the abnormal methylation of *BRCA1* promoter in WBC as a powerful non-invasive molecular marker for detecting predisposed individuals at a very early age.[73]

Another study done in Saudi Arabia associated between amplified risk of breast cancer and the *PARP-1 Val762Ala* (rs1136410) genotype. These findings suggested that *PARP-1 Val762Ala* may adapt the episode of *PARP1* mutations and donated to breast carcinogenesis. Their findings suggested that *PARP-1Val762Ala* variation may play an important role in the advance of breast carcinoma. In spite of their data supports for a clear relationship between *PARP1* and breast cancer in Saudi inhabitants and *PARP1* gene plays a major role in the vulnerability to the disease.[84]

In the other hand, study published in 2013 regarding polymorphisms of breast cancer susceptibility gene *BRCA1* (rs799917) and *BRCA2* (rs144848) found no statistically significant correlation with clinico-pathological characteristics of breast cancer. Hence, they concluded that genetic polymorphisms in *BRCA1* (rs799917) and *BRCA2* (rs144848) could not play any role in the development of the breast cancers in the Saudi inhabitants. However a study with a larger sample number is before a firm conclusion about no role of these variants in breast cancer predisposition.[85]

In some other study which published in 2013, the researchers investigated whether the *MMP-2 SNP* was linked with susceptibility to breast cancer in the Saudi inhabitants. Approximately ninety breast cancer patients and 92 age matched controls were included in this study. For the genotyping TaqMan Allele Discrimination method and DNA sequencing techniques were used. The results confirmed that, the presents of *MMP-2 CC* wild genotype was lower in breast cancer patients when compared with controls. The study indicated that the *MMP-2* $C_{-1306}T$ polymorphism will be informative in tests of associations for breast cancer.[14]

Some study done in Riyadh to examine the detection of mutation of *PIK3CA* in Arab breast cancers. The results obtained were comparable to the universal standard and the occurrence of these mutations may favor patient endurance. Additionally, there were no *PIK3CA* somatic mutations in breast CAFs that were analyzed. Furthermore, they reported a high association of the *SNP rs17849079* amongst Arab breast cancer patients compared with controls, which suggests its probable utilize as a breast cancer vulnerability and early molecular marker diagnostic for this inhabitants.[86]

A relationship studies examining interactions of gene-gene were necessary to explain exploration of the result of two *rs25487* (Arg399Gln) polymorphisms in *XRCC1* and non-synonymous *SNPs, rs1799782* (Arg194Trp) with consider to the risk of increasing breast cancer in the Saudi inhabitants, and it remains probable that *XRCC1* unpredictability may involve disease sequence or the vulnerability to increase breast cancer. Verification of their result in larger populations of vary ethnicities would give confirmation for the responsibility of *XRCC1* gene in breast carcinomas.[87]

Some study suggested that *PARP-1* dysfunction may participate in an essential role in the growth of breast carcinoma. Regardless of their data supports for a obvious relationship between *PARP1* and breast cancer in Saudi inhabitants and *PARP1* gene plays a main role in the vulnerability to the disease.[88]

In 2013 some other study utilized pathway supported approach to recognize involvement of risk alternatives in the *Wnt* signaling pathway genes with breast cancers. Substantiation of their findings in the *SNP* in β-catenin gene which was linked with amplified risk of breast cancers.[89]

The author of this review had previous study regarding the association of gene detection with breast cancer. However, the study found that the *p53* and *p63* genes was positive in case of breast cancer, especially within the age group 30-60 years old and with grade II, III. In conclusion, *p53* is rarely co expressed with *p63*, suggesting that *p63* could act indirectly as an oncogene by inhibiting *p53*.[90]

In a case control study done in Saudi Arabia in 2012; the study suggested that genotype AA for *TNF-a* (rs1800629) A⁄G and both GG as well as TT genotype for *IL6* (rs1554606) G⁄T may be risk factors due to defeat of heterozygosity (LOH) in case of breast cancer in a Saudi inhabitants.[91]

Similar case control performed using TaqMan-based real-time PCR in patients with breast cancer and healthy controls in Saudi inhabitants. These results demonstrated an enlarged risk of breast cancer connected with the *MDM2* GG genotypes and with the *TP53* Pro/Pro genotype. These results suggested that polymorphisms of *MDM2* and *TP53* genes may be a genetic modifier for rising breast cancer in these ethnic inhabitants in the Arab world.[92]

Similar study indicated that *bcl2* genes polymorphism were likely associated with breast cancer data and this polymorphism might be a candidate for the genetic marker to screen the risks of breast cancer.[93]

CONCLUSION

Gene mutations regarding breast cancer are promising field in Saudi Arabia. Although there are several studies done, but still epidemiological complementary and comprehensive study is desirable to concentrate on the gene mutations that found significantly positive in Saudi community. Particularly, some studies done confirmed that Saudi women were very interesting in testing for breast cancer genetically to avoid the late stage of the disease and early detection of the disease may lead to good prognosis.

REFERENCES

1. Chouchane L, Boussen H, Sastry K. Breast cancer in Arab populations: molecular characteristics and disease management implications. Lancet Oncol 2013; 14: e417–24.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893–917.
3. Curado MP. Breast cancer in the world: Incidence and mortality. Salud Publica Mex 2011; 53: 372-384.
4. El Saghir N, Khalil M, Eid T, El Kinge A, Charafeddine M, Geara F, Seoud M, Shamseddine A. Trends in epidemiology and management of breast cancer in developing Arab countries: A literature and registry analysis. Inter. J. Surg. 2007; 5, 225e233.
5. Tehranian N, Shobeiri F, Pour F, Hagizadeh E. Risk Factors for Breast Cancer in Iranian Women Aged Less than 40 Years. Asian Pacific J Cancer Prev, 2010; 11: 1723-1725.
6. Amin TT, Al-Wadaani HA, Al-Quaimi MM, Aldairi NA, Alkhateeb JM, Al-Jaafari AA. Saudi women's interest in breast cancer gene testing: possible influence of awareness, perceived risk and socio-demographic factors. Asi Pac J Can. Prev. 2012; 13(8): 3879-87.
7. Radi **S.** Breast Cancer Awareness among Saudi Females in Jeddah. Asian Pac J Cancer Prev, 14(7): 4307-4312.

8. Al Diab A, Qureshi S, Al Saleh K, Al Qahtani F, Aleem A, Alghamdi M, Alsaif A, Bokhari A, Qureshi V, Qureshi M. Review on Breast Cancer in the Kingdom of Saudi Arabia. Mid. Eas. J Scien. Rese. 2013; 14(4): 532-543.
9. Eittah H, Awed H, Bukhary Z. Effect of Health Education on Raising Female Students Awareness' Regarding Breast Cancer at Saudi Arabia. Journal of Natural Sciences Research, 2014; 4(9).
10. Saudi Cancer Registry. http://www.scr.org.sa/files/file/2010.pdf
11. Ibrahim EM, Zeeneldin AA, Sadiq BB, Ezzat AA. The present and the future of breast cancer burden in the Kingdom of Saudi Arabia. Med. Onco. 2008; 25(4): 387-93.
12. Gaballah I. Awareness, Knowledge and Practice of Breast Self-Examination Among Saudi Women. Med. J. Cairo Univ. 2011; 79(2): 81-86.
13. Elkum N, Dermime S, Ajarim D, Al-Zahrani A, Alsayed A, Tulbah A, Al Malik O, Alshabanah M, Ezzat A, Al-Tweigeri T. Being 40 or younger is an independent risk factor for relapse in operable breast cancer patients: the Saudi Arabia experience. BMC Cancer, 2007; 5(7): 222.
14. Saeed H, Alanazi M, Alshahrani O, Parine N, Alabdulkarim H, Shalaby M. Matrix metalloproteinase-2 C-^{1306}T promoter polymorphism and breast cancer risk in the Saudi population. ABP. 2013; (60)3: 405–409.
15. Anderson BO, Braun S, Carlson RW, Gralow JR, Lagios MD, Lehman C, Schwartsmann G, Vargas HI. Overview of breast health care guidelines for countries with limited resources. Breast J. 2003; 2(9): S42e5035.
16. Kelsey JL, Horn-Ross PL. Breast cancer: magnitude of the problem and descriptive epidemiology. Epidemiologic reviews, 1993, 15(1): 7–16.
17. Ravichandran K, Al-Zahrani AS. Association of reproductive factors with the incidence of breast cancer in Gulf Cooperation Council countries. East Med. Heal J., 2009; 15(3): 612-621.
18. Di Cosimo S, Baselga J. Management of breast cancer with targeted agents: importance of heterogeneity. Nat Rev Clin Oncol, 2010; 3: 139-47.
19. Ban KA, Godellas CV. Epidemiology of breast cancer. Surg Oncol Clin N Am, 2014; 3: 409-22.

20. Khabaz MN. Immunohistochemistry Subtypes (ER/PR/HER) of Breast Cancer: Where Do We Stand in the West of Saudi Arabia? Asian Pac J Cancer Prev, 2015; 15(19): 8395-8400.
21. Prat A, Perou CM. Deconstructing the molecular portraits of breast cancer. Mol Oncol, 2011; 1: 5-23.
22. Tamimi RM, Colditz GA, Hazra A, Baer HJ, Hankinson SE, Rosner B, Marotti J, Connolly JL, Schnitt SJ, Collins LC.Traditional breast cancer risk factors in relation to molecular subtypes of breast cancer. Breast Cancer Res Treat, 2012; 1: 159-67.
23. Fasching PA, Pharoah PD, Cox A, Nevanlinna H, Bojesen SE, Karn T, et al., The role of genetic breast cancer susceptibility variants as prognostic factors. Hum Mol Genet 2012; 21: 3926–3939.
24. Kolberg HC, Luftner D, Lux MP, Maass N, Schutz F, Fasching PA, Fehm T, Janni W, Kümmel S. Breast cancer 2012 – new aspects. Geburtshilfe Frauenheilkd 2012; 72: 602–615.
25. Schmidt M, Fasching PA, Beckmann MW, Kolbl H. Biomarkers in breast cancer – an update. Geburtshilfe Frauenheilkd. 2012; 72: 819–832.
26. Anderson B, Ilbawi A, El Saghir N. Breast Cancer in Low and Middle Income Countries (LMICs): A Shifting Tide in Global Health. The Brea J., 2015; 21(1): 111–118.
27. Najjar H, Easson A. Age at diagnosis of breast cancer in Arab nations. Intern. J. of Surg. 2010; 8: 448-452.
28. Harhra N, Basaleem H. Trends of Breast Cancer and its Management in the Last Twenty Years in Aden and Adjacent Governorates, Yemen. Asian Pacific J Cancer Prev, 13(9): 4347-4351.
29. Mehdi I, Monem EA, Al Bahrani B J, Al Kharusi S, Nada AM, Al Lawati J, Al Lawati N. Age at diagnosis of female breast cancer in Oman: Issues and implications. South Asian Journal of Cancer, 2014; 3(2): 101–106.
30. Al-Qahtani MS. Gut metastasis from breast carcinoma. Saudi Medi J, 2007; 28: 1590-2.
31. Altaf FJ, Abdullah LS, Jamal AA. Frequencey of Benign and preinvasive breast diseases. Saudi Med J 2004; 25(4): 493-497.

32. Altaf FJ. Breast Cancer Screening. Saudi Med J 2004; 25(8): 991-997.
33. Ravichandran K, Hamdan N, Dyab A, Population based survival of female breast cancer cases in Riyadh Region, Saudi Arabia. Asian Paci J. of Can Preve, 2005; 6: 72-6.
34. Al-Rikabi A, Husain S. Increasing prevalence of breast cancer among Saudi patients attending a tertiary referral hospital: a retrospective epidemiologic study. Croatian Medical Journal 2012; 53(3): 239-243.
35. Abolfotouh MA, Abulkhair O, Sbitan SE, Ahmad F, Al-Muammar MN. Dietary Fat Intake, Serum Estrogen Level and Obesity as Risk Factors of Breast Cancer in Saudi Females: A Case-Control Study. British Journal of Medicine & Medical Research, 2013; 3(3): 698-709 a.
36. Abolfotouh MA, Abulkhair O, Sbitan SE, Ahmad F, Al-Muammar MN. Case- control Study of Breast Cancer and Dietary Fat Intake in Saudi Females. J Womens Health, 2013; 2(5): b.
37. Hasan M, Al Zohairy M, Mohieldein A. Diabetic type 2 and breast cancer marker CA 15.3 value. European Journal of Experimental Biology, 2014; 4(2): 178-181.
38. Alghamdi IG, Hussain II, Alghamdi MS, El-Sheemy MA. The incidence rate of female breast cancer in Saudi Arabia: an observational descriptive epidemiological analysis of data from Saudi Cancer Registry 2001–2008. Breast Cancer: Targets and Therapy 2013; 5: 103–109.
39. ESHRE Capri Workshop Group. Hormone and breast cancer. Hum Re-prod update 2004; 10:281-93.
40. Albrektsen G, Heuch I, Hansen S, Kvåle G. Breast cancer risk by age at birth, time since birth and time intervals between births: Exploring interaction effects. BRJ Cancer 2005; 92: 167-75.
41. Gennari R, Curigliano G, Rotmensz N, Robertson C, Colleoni M, Zurrida S, Nolè F, de Braud F, Orlando L, Leonardi MC, Galimberti V, Intra M, Veronesi P, Renne G, Cinieri S, Audisio RA, Luini A, Orecchia R, Viale G, Goldhirsch A. Breast carcinoma in elderly women: features of disease presentation, choice of local and systemic treatments compared with younger postmenopasual patients. Cancer. 2004 Sep 15; 101(6): 1302-10.

42. Washbrook E. Risk factors and epidemiology of breast cancer. BREAST CANCER. WOMEN'S HEALTH MEDICINE 3:1. 2006 Elsevier Ltd: 8-14.
43. Saudi Cancer Registry. http://www.scr.org.sa
44. El Hag IA, Katchabeswaran R, Chiedozi LC, Kollur SM. Pattern and incidence of cancer in Northern Saudi Arabia. Saudi Med J 2002; 23: 1210e3.
45. Al-daihan S, Shafi R. Breast Cancer in Saudi Arabia: A Review. Inter. J. Biotech. and Bioch. 2012; 8(1): 71-77.
46. Ezzat A, Raja MA, Berry J, Zwaan FE, Jamshed A, Rhydderch D, Rostom A, Bazarbashi S. Impact of pregnancy on nonmetastatic breast cancer: a case control study. Clin. Oncol., 1996; 8: 367-70.
47. Khairy GA, Al-Abdulkarim HA. Breast carcinoma during pregnancy. Saudi Medical Journal. 2008; 29: 1662-5.
48. Al-Idrissi HY.. Pattern of breast cancer in Saudi females in eastern province of Saudi Arabia. Indi J Med Scie, 1991; 45: 85-7.
49. Al-Idrissi HY, Ibrahim EM, Kurashi NY, Sowayan SA,. Breast cancer in a low risk population. The influence of age and menstrual status on disease pattern and survival in Saudi Arabia. Inter. J. Canc., 1992; 52: 48-51.
50. Alothaimeen A, Ezzat A, Mohamed G, Muammar T, Al-Madouj A. Dietary fat and breast cancer in Saudi Arabia: a case-control study. East MeditHeal J, 2004; 10: 879-86.
51. Arif JM, Al-Saif AM, Al-Karrawi MA, Al-Sagair OA. Causative relationship between diabetes mellitus and breast cancer in various regions of Saudi Arabia: an overview.Asian Paci. J. of Can. Preve., 2011; 12: 589-92.
52. Alokail MS, Al-Daghri NM, Al-Attas S, Hussain T. Combined effects of obesity and type 2 diabetes contribute to increased breast cancer risk in premenopausal women. Cardiovascular Diabetology, 2009; 8: 33.
53. Elkum N, Al-Tweigeri T, Ajarim D, Al-Zahrani A, Bin Amer S, Aboussekhra A. Obesity is a significant risk factor for breast cancer in Arab women. BMC Cancer 2014; 14: 788.
54. Bottorff JL, Ratner PA, Balneaves LG, Richardson CG, McCullum M, Hack T, Chalmers K, Buxton J. Women's interest in genetic testing for breast cancer risk: the

influence of socio-demographics and knowledge. Cancer Epidemiol Biomarkers Prev, 2002; 11: 89–95.

55. Kinney AY, Gammon A, Coxworth J, Simonsen SE, Arce-Laretta M. Exploring attitudes, beliefs, and communication preferences of Latino community members regarding *BRCA1*/2 mutation testing and preventive strategies. Genet Med, 2010; 12: 105–115.
56. Meleis AI, Hattar-Pollara M, Arab Middle Eastern American women: stereotyped, invisible, but powerful. In: Adams DL, editor. Health issues for women of color: a cultural diversity perspective. Thousand Oaks: SAGE Publications; 1995; 133-163.
57. Al-Gazali L. Attitudes toward genetic counseling in the United Arab Emirites. Community Genetics.2005; 8(1): 48–51.
58. Azaiza F, Cohen M. Between traditional and modern perceptions of breast and cervical cancer screening: a qualitative study of Arab women in Israel. Psycho-Oncology. 2008; 17: 34–41.
59. Shah SM, Ayahs C, Pharaon NA, Gany FM. Arab American immigrants in New York: health care and cancer knowledge, attitudes, and beliefs. J Immig. Min. Heal. 2008; 10: 429–436.
60. Banning M, Hafeez H, Faisal S, Hassan M, Zafar A. The impact of culture and sociological and psychological issues on Muslim patients with breast cancer in Pakistan. Cancer Nursing. 2009; 32(4): 317–324.
61. Carlson RW, Allred DC, Anderson BO, Burstein HJ, Carter WB, Edge SB, Erban JK, Farrar WB, Forero A, Giordano SH, Goldstein LJ, Gradishar WJ, Hayes DF, Hudis CA, Ljung BM, Mankoff DA, Marcom PK, Mayer IA, McCormick B, Pierce LJ, Reed EC, Sachdev J, Smith ML, Somlo G, Ward JH, Wolff AC, Zellars R. Invasive breast cancer. J Natl Compr Canc Netw 2011; 9: 136–222.
62. Masood S, Vass L, Ibarra JA Jr, Ljung BM, Stalsberg H, Eniu A, Carlson RW, Anderson BO. Breast pathology guideline implementation in low- and middle-income countries. Cancer 2008; 113(8): 2297–304.
63. Anderson BO. Breast Cancer—Thinking Globally. Science; 2014; 343: (6178).

64. Carlile T, Kopecky KJ, Thompson DJ, Whitehead JR, Gilbert FI Jr, Present AJ, Threatt BA, Krook P, Hadaway E. Breast Cancer prediction and the Wolfe Classification of mammograms. JAMA 1985; 254: 1050-1053.
65. Smith RA, Saslow D, Sawyer KA, Burke W, Costanza ME, Evans WPAmerican Cancer Society guidelines for breast cancer screening: update 2003. CA Cancer J Clin 2003; 53: 141-169.
66. Alsaif A. Breast self-examination among saudi female nursing students in saudi arabia. Breast Cancer Researches in Saudi Arabia. 2010; 1(1): 25-29.
67. American Cancer Society. Cancer statistics. CA: Am Cancer J Clin 2002; 52: 10-11.
68. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, DingW, Bell R, Rosenthal J, Hussey C, Tran T, McClure M, Frye C, Hattier T, Phelps R, Haugen-Strano A, Katcher H, Yakumo K, Gholami Z, Shaffer D, Stone S, Bayer S, Wray C, Bogden R, Dayananth P, Ward J, Tonin P, et al: A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1*. Science (New York, NY) 1994; 266(5182): 66–71.
69. Martin AM, Weber BL. Genetic and Hormonal Risk Factors in Breast Cancer. Journal of the National Cancer Institute, 2000; 92:(14), 1126-1135.
70. Arver B, Du Q, Chen J, Luo L, Lindblom A: Hereditary breast cancer: a review. Semin Cancer Biol 2000; 10(4): 271–288.
71. Petrucelli N, Daly MB, Feldman GL. BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer. GeneReviews; 2013. Bookshelf. http://www.ncbi.nlm.nih.gov/books
72. Snell C, Krypuy M, Wong EM, Con Fabi K, Loughrey MB, Dobrovic A: *BRCA1* promoter methylation in peripheral blood DNA of mutation negative familial breast cancer patients with a *BRCA1* tumour phenotype. Breast Cancer Res 2008; 10(1): R12.
73. Al-Moghrabi N, Nofel A, Al-Yousef N, Madkhali S, Bin Amer S, Alaiya A. The molecular significance of methylated BRCA1 promoter in white blood cells of cancer-free females. BMC Cancer 2014; 14: 830.
74. Al-Moghrabi N, AL Qasem A, Aboussekhr A. Methylation-related mutations in the BRCA1 promoter in peripheral blood cells from cancer-free women. Intern. J. of oncology 2011; 39: 129-135.

75. Cho Y, Yazici H, Wu H, Terry M, Gonzalez K, Qu M, Dalay N, Santella R M. Aberrant Promoter Hypermethylation and Genomic Hypomethylation in Tumor, Adjacent Normal Tissues and Blood from Breast Cancer Patients. Anticancer Research, 2010; 30: 2489-2496.
76. Lee MS, Green R, Marsillac SM Williams RS, Yeung T, Foo D, Hau DD, Hui B, Monteiro AN, Glover JN. Comprehensive analysis of missense variations in the BRCT domain of *BRCA1* by structural and functional assays. Cancer Res 2010; 70(12): 4880–4890.
77. Coquelle N, Green R, Glover JN. Impact of *BRCA1* BRCT domain missense substitutions on phosphopeptide recognition. Biochemistry 2011; 50(21): 4579–4589.
78. Greenberg RA (2011) Cancer. *BRCA1*, everything but the RING? Science 334(6055): 459–460.
79. Biunno I, Aceto G, Awadelkarim K, Morgano A, Elhaj A, Eltayeb E, Abuidris D. BRCA1 point mutations in premenopausal breast cancer patients from Central Sudan. Familial Cancer. 2014; 13:437-444.
80. El-Harith A, Abdel-Hadi M, Steinmann D, Dork T. *BRCA1* and *BRCA2* mutations in breast cancer patients from Saudi Arabia. Saudi Med J 2002; 23(6): 700-704.
81. Vadaparampil ST, McIntyre J, Quinn GP: Awareness, perceptions, and provider recommendation related to genetic testing for hereditary breast cancer risk among at-risk Hispanic women: similarities and variations by sub-ethnicity. J Genet Couns; 2010; 19(6): 618-29.
82. Shiovitz S and Korde LA. Genetics of Breast Cancer: A Topic in Evolution. Annals of Oncology Advance Access published January 20, 2015.
83. Nemenqani D, Karam R, Amer M, Abd El Rahman T. Vitamin D receptor gene polymorphisms and steroid receptor status among Saudi women with breast cancer. Gene 2015; 558: 215–219.
84. Alanazi M, Pathan A, Shaik J, Al Amri A, Parine N. The C Allele of a Synonymous SNP (rs1805414, Ala284Ala) in PARP1 is a Risk Factor for Susceptibility to Breast Cancer in Saudi Patients. Asian Pac J Cancer Prev, 2013; 14(5): 3051-3056.
85. Hasan T, Shafi G, Syed N, Alsaif A, Alsaif A, Alshatwi A. Lack of Association of *BRCA1* and *BRCA2* Variants with Breast Cancer in an Ethnic Population of Saudi

Arabia, an Emerging High-Risk Area. Asian Paci. J. of Canc Preven., APJCP.2013; 14(10): 5671-5674.

86. Karakas B, Colak D, N Kaya, Ghebeh H, Al-Qasem A, Hendrayani F, Toulimat M, Al-Tweigeri T, Park B, Aboussekhra A. Prevalence of PIK3CA mutations and the SNP rs17849079 in Arab breast cancer patients. Cancer Biology & Therapy 2013; 14:10, 888–896.
87. Al Mutairi F, Alanazi M, Shalaby M, Alabdulkarim H, Pathan A, Parine N. Association of XRCC1 Gene Polymorphisms with Breast Cancer Susceptibility in Saudi Patients. APJCP, 2013; 14(6): 3809-3813.
88. Alanazi M, Pathan AAK, Arifeen Z, Shaik JP, Alabdulkarim HA, Semlali A, BazziM , Parine N. Association between PARP-1 V762A Polymorphism and Breast Cancer Susceptibility in Saudi Population. PLoS ONE 2013; 8(12): e85541.
89. Alanazi MS, Parine NR, Shaik JP, Alabdulkarim HA, Ajaj SA, Khan Z. Association of Single Nucleotide Polymorphisms in Wnt Signaling Pathway Genes with Breast Cancer in Saudi Patients. PLoS ONE 2013; 8(3): e59555.
90. Babalghith A. P53 and P63 as Associated Molecular Markers in Breast Cancer in Saudi Arabia Patients. UQU Medical Journal. 2012; 3(2): 83-90.
91. Alshatwi A, Hasan T, Shafi G, Alsaif A, Aldiab A, Alsaif M, Al-Hazzani A, Lei K. Genetic Variation in IL-6 and TNF-a Genes with Risk of Breast Cancer in a Saudi Population-based Case–Control Study. The Breast Journal, 2012; 18(4): 383-385.
92. Alshatwi A, Hasan N, Shafi G, Alsaif A, Al-Hazzani A, Alsaif A. A single-nucleotide polymorphism in the TP53 and MDM-2 gene modifies breast cancer risk in an ethnic Arab population. Fundam Clin Pharmacol. 2012; 26(3): 438-43.
93. Alshatwi A, Shaf G, Hasan N, Alsaif A, Al-Hazzani A, Alsaif A, Lei K. Single nucleotide polymorphisms in the p21 and bcl2 cancer susceptibility genes and breast cancer risk in Saudi Arabia. Asian Pac J Cancer Prev. 2011; 12(10): 2607-10.