Review on Breast Cancer in the Kingdom of Saudi Arabia

Abdurrahman Al Diab, Shoeb Qureshi, Khalid A. Al Saleh, Farjah H. Al Qahtani, Aamer Aleem, Mohammed A. Alghamdi, A. Alsaif, Areej A. Bokhari, Viquar Fatima Qureshi and Mohammad Rehan Qureshi

Oncology Division, Department of Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia
College of Medicine, Salman bin Abdulaziz University, Alkharj, Saudi Arabia
Department of Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia
Department of Obstetrics and Gynecology, College of Medicine, King Saud University, Riyadh, Saudi Arabia
Department of Surgery, Deccan College of Medical Sciences, Hyderabad, India

Abstract: Breast Cancer (BC) is considered the most implacable malignancy and the leading cause of mortality in the Kingdom of Saudi Arabia (KSA). The literature on different aspects of BC is rich in contributions from developed and Western countries. Nevertheless, despite substantial individual efforts, the views of experts from KSA lack a collective portrayal. Hence, an attempt has been made to gather together the information in the form of an overview which includes some facets of BC. The views of experts from Saudi Arabia on these aspects of BC in the Kingdom included an amalgamation of a variety of articles published during last more than thirty years from different research and teaching institutions. The task was met up with peer reviewed English language articles cited in Pub Med, Pub Med Central, Science Direct, Up-to-date, Med Line, Comprehensive data bases, Cochrane library and the internet (Google, Yahoo). The study provides impetus on further analysis of the association between epidemiology, knowledge of BC and practice of breast self-examination (BSE), etiological factors, metastases and rate of survival. Further studies are warranted to enrich the information for planning of screening, management and preventive strategies of BC in KSA, which may indirectly benefit worldwide health care.

Key words: Breast Cancer • Epidemiology • Knowledge of BSE • Etiology • KSA

INTRODUCTION

Breast Cancer (BC) has a major impact on health of women worldwide and the KSA is no exception. It is considered the most common malignancy and represents the second leading cause of cancer deaths after lung cancer. The malignancy carries tremendous socio-economic, emotional and public health implications. Most of the available literature on different aspects of BC is reported from developed nations and Western countries, while; data on relevant reports from Saudi Arabia appears either scattered or not brought to limelight. This study provides an overview of BC incidence reported from different hospitals in KSA and constitutes different aspects including epidemiology, knowledge of BC and practice of BSE, etiological factors, metastases and rate of survival. As a baseline, the study would provide knowledge to enrich the information for planning of screening, management and preventative strategies of BC in KSA, which may indirectly benefit worldwide health care.

MATERIALS AND METHODS

The present study on the views of experts from Saudi Arabia on different facets of BC in the Kingdom included the information from articles published during the last more than thirty years from different research and
teaching institutions. Publications selected comprised some of the different aspects of BC, including epidemiology, knowledge of BC and practice of BSE, etiological factors, metastases and rate of survival published by different research institutions of KSA. The task was met up with peer reviewed English language articles cited in Pub Med, Pub Med Central, Science Direct, Up-to-date, Med Line, Comprehensive data bases, Cochrane library and the internet (Google, Yahoo). The strategy of search combined terms that included the title and the keywords.

Review of Literature: The present study is a continuation of our work on an overview relating methods of diagnosis and biomarkers used in early detection of BC in KSA [1] and another review which concerns the preventive and chemotherapeutic strategies of BC in KSA which is in the stage of submission. The present study is a systematic collection of literature on published papers from different institutions, hospitals and research centers of KSA that includes (1) epidemiology of breast cancer in KSA (2) knowledge of BC and practice of BSE (3) etiological factors and (4) metastases and rate of survival and (5) conclusion.

Epidemiology of Breast Cancer in Ksa

Incidence of BC: Breast Cancer is the second most common cancer in the world. A report of the American Cancer Society showed about 1.3 million American women are annually diagnosed with BC and about 0.5 million die from the malignancy [2]. KSA is no exception, where cancer of breast is most commonly prevalent. In one of the epidemiological studies conducted, Ravichandran et al. [3] reported the incidence of BC in KSA was 19.8% of all the female cancers detected in the Kingdom. Al-Qahtani [4] showed BC as the second most common malignancy in women in KSA. Nevertheless, there is a paucity of detailed published epidemiologic data and an updated account of the figures registered. An earlier report according to Saudi National Cancer Registry reported an increasing proportion of BC among women of different ages from 10.2% (2000) to 24.3% (2005) [5]. Ravichandran and Al-Zahrani [6] investigated the incidence of female BC in the Gulf Cooperation Council (GCC) countries in relation to the established reproductive factors. A total of 4480 BC cases were diagnosed in women during 1998-2002 among GCC country nationals. BC was the most common malignancy ranging from 16.1% Oman to 35.4% in Bahrain. The age-standardized incidence rate per 100,000 was highest in Bahrain (46.4), followed by Kuwait (44.3), Qatar (35.5), United Arab Emirates (19.2), Oman (14.4) and Saudi Arabia (12.9). These rates are low compared with most industrialized Western countries. According to a report of Saudi National Cancer Registry (2000-2004), the incidence of BC was 127.8 per 100,000 women and the mortality rate was reported as 25.5 per 100,000 [7].

A total of 7251 histologically confirmed new cases of cancer (4117 males and 3134 females) were seen in the 6-year period (1979 to 1984) in Riyadh. The study analyzed frequencies of cancer at different primary sites, including non-Hodgkin's lymphomas, esophagus, lung, liver, stomach and nasopharynx among the males. Nevertheless, BC was the most common tumor among the females, followed by non-Hodgkin's lymphomas and cancers of the thyroid, esophagus, cervix and ovary [8]. Al-Idrissi [9] investigated the pattern of BC in Saudi females in Alkhobar (eastern province). A total of 1,658 Saudi nationals with different malignant conditions were admitted. Out of this 69 (4.1%) females suffered from BC. The author concluded that the incidence of BC among Saudi women is low, multiparous and breast feeding does not give any protection to the patients. In a study on pattern of cancer in Abha, Khan et al. [10] investigated a total of 697 histologically confirmed cases of cancer seen in a three-year period (1987 to 1989). In females, BC was most common cancer, next to skin. Ajarim [11] found BC as the leading malignancy among 471 females in Riyadh. In a study on profile of cancer in Riyadh, Korieh and Kuhaymi [12] found BC as the most frequent malignancy in females, accounting for 24% of all the female cancers, Inspite of the infrequency of the traditional risk factors of nulliparity, late age of first pregnancy, late age of menopause and high dietary fat consumption. Two-thirds of patients with BC were premenopausal. Twelve females with cystosarcomaphyllodes of the breast were referred to a specialist hospital in Riyadh between 1980 and 1990, representing 0.8% of BC patients. The median age was 45 years. Seven patients (58%) were premenopausal. All the patients presented with breast mass, measuring >10 cm in 58% of them. The median duration of symptoms was 15 months. At presentation, neither axillary lymph nodes nor distant metastases were seen. Surgery with a follow up of chemotherapy was done [13]. Al-Saigh et al. [14] analyzed the pattern of cancer in Madina Al-Munawara in a retrospective study of 2237 histologically proven cases of cancer over a period of 12 year (1981 to 1993). Of the 2237 cases the frequency of BC was 8.5%. It was the leading cancer among females.
In a report on the first population-based tumor registry in the Eastern region, Al Tamimi et al. [15] showed that the age-specific rate, crude incidence rate (CIR), age-standardized incidence rate (ASR) among Saudi females in Eastern region were 43.6 and 95.5, respectively, which are very low on an international scale. The cancer sites with the highest percent of ASR among Saudi females were breast, leukemia, tumors of brain and nervous system and thyroid. The overall cancer (ASR) in the Eastern region was found to be low as reported in the first Regional Population-Based Cancer Registry in Saudi Arabia that was established in 1987. The leading cancer site with highest percent ASR was breast among Saudi females. In an overview of BC, Ezzat et al. [16] reported that a total of 1584 female BC patients were treated in Riyadh between 1975 and 1991. Early BC (Stages I, II) represented 36%, while 64% presented with advanced or metastatic disease (Stages iii, iv). The majority of patients were premenopausal (64%). In another study, data on female patients with invasive BC was analyzed on 292 patients between 1985 and 1995 in Eastern Province. Most of the patients were below 50 years of age (78%) and were predominantly pre-menopausal (79%). Only 25 (9%) had stage I cancer, while 130 (44%), 90 (30%) and 47 (16%) had stage II, III and IV respectively. The study involved chemotherapeutic strategies [17]. Studies on BC in Saudi Arabia from a specialist hospital in Riyadh showed that the incidence of BC constitutes 18% of all cancers in Saudi women; locally advanced BC is more than 40% of all non-metastatic BC in the KSA [18].

Archibong et al. [19] undertook a study to compare the frequencies of various types of malignant neoplasm's affecting females (274) in Asir Region during the years 1996-1998. Histopathological records of various types revealed breast malignancies (22%) as leading. Although the rates for female breast diseases varied in different studies, benign fibroadenoma was the most common breast lesion followed by ductal carcinoma as revealed in a study conducted on 953 female breast biopsies and mastectomies in Jeddah [20]. El Hag et al. [21] investigated the record of all confirmed cancer cases retrieved and studied from files of the Histopathology and Cytology Department in Al-Jouf and found BC to be the most common cancers in the whole population. In the same hospital, Chiedozi et al. [22] reviewed the histological and clinical records of 708 patients. Breast diseases were common among these patients. Although benign disease is the most common, some had small lesions with a definite cancer risk. Of great concern was the pattern of advanced BC, which presents mostly in premenopausal women of younger age.

Histopathological records of 2129 breast cases including mastectomies and breast biopsies during 1985 to 2002 were reviewed in Jeddah. The results of the study showed that the percentage of benign non-proliferative diagnosis was 85.3% that was higher than the literature 69.7%. Proliferative diseases were 9.3% and atypical hyperplasia was 0.5%, which was much less than the literature (26.2% and 3.6%). On the other hand, CIS diagnosis was 4.9%, which was much higher than the reported literature (1.7%). The study clearly points a higher prevalence of benign breast lesions in this population [23].

From a random record of different hospitals in KSA, Mansoor, [20] investigated 953 female breast biopsies and mastectomies. In this study, outline of breast lesions were classified into inflammatory, benign and malignant lesions. The rates for female breast diseases were variable but benign fibroadenoma was the most common breast lesion followed by ductal carcinoma. Over a 975 registered visits in Dammam, between 1997-2007, 303 cases were diagnosed with breast malignancy. An insight into the patients’ records identified considerable delay of 6-15 weeks before resuming the final care [24].

In a report on BC statistics during 1998 to 2004, Saadat, [25] found that the GCC states were found to have a total of 6,882 cases that accounted to 11.8% from all cancers and 22.7% from cancers in women. An analysis per 100,000 females showed 46.4 from Bahrain, 44.3 from Kuwait, 35.5 from Qatar, 19.2 from UAE, 14.2 from Oman and 12.9 from KSA. The study demonstrated BC incidence as the lowest in KSA among all the GCC states. Histopathology records of 969 patients in Al Hassa, Hofuf were reviewed between January 2001 and December 2007. The records showed benign lesions (60.1%), malignancy (21.4%), inflammatory lesions (18.5%), multiple benign lesions (51.1%), > two lesions (21.1%). Benign breast lesions multiplicity was quite common among Saudi female patients [26].

In a recent report, Al-Rikabi and Husain [27] presented a review of breast biopsy reports of a mass or lump from male and female patients seen between January 2001 and December 2010 in Riyadh. Of the 1035 breast tissues reviewed, 345 (34.2%) malignant cases were found. In men 9.4% were malignant and in women, 336 (35.8%) were malignant. The malignant cases from male patients belonged to invasive ductal carcinoma and majority of malignant cases from female patients belonged to invasive/infiltrating ductal carcinoma. The annual percentage incidence of malignant BC was found to increase by 4.8% in 2007 from an annual rate of 23.5% in 2000. Medical records of 262 female patients in Al Khobar
with confirmed diagnosis of invasive BC were reviewed for a comparison with published data from the United States. The data suggested that BC in Alkhobar is diagnosed at a much higher stage compared to the United States. Al-Tamimi et al. [31] analyzed the spectrum of molecular subtypes using ER, PR, HER2, EGFR and CK5/6 as surrogate markers for gene expression profiling to classify the 231 BC specimens. The correlation of each molecular class with Ki-67 proliferation index, p53 mutation status, histologic type and grade of the tumor was also performed. Results of the study demonstrated a prevalence pattern that is unique to Saudi population; luminal tumors (19.9%) and the unclassified group (penta negative, 42.8%), a distribution which is specific to Saudi population and is in contrast with the Western studies.

Prevalence of BC at Molecular Level: There is an increasing evidence to suggest the possibility of molecular differences between BC from different ethnic groups. BC is not a single unit but a diverse group of entities. Advances in gene expression profiling and immunohistochemistry have led to revelation of new BC molecular subtypes, resulting in the emergency of a more elaborate classification systems that are therapeutically and prognostically more predictive. Literature reports suggest substantial differences in the molecular patterns of cancers from various ethnic groups. Since these patterns are increasingly used to predict cancer prognosis and response to therapy, better knowledge of ethnic molecular features is important. In order to identify molecular differences between BCs in Europe and the Middle East, Al-Kuraya et al. [29] analyzed consecutive BC series from Switzerland (2197) and Saudi Arabia (204). Tissue microarrays were analyzed by fluorescence in situ hybridization for HER2, CCND1, MYC and EGFR amplification. The data showed prominent differences between Saudi and Swiss patients. Saudi BCs had a higher frequency of HER2 and MYC amplifications than Swiss BCs. This appears to be due to a much higher incidence of grade 3 cancers in the Saudi than in the Swiss population. However, in combination with known age incidence rates of BC in Saudi Arabia (21.6/100 000) and Switzerland (70.1/100 000), these data suggest that the incidence of high-grade BC is comparable for Saudi and Swiss women, while the incidence of low-grade BCs is about 14 times lower in Saudi than for Swiss women. These results suggest that a difference in genetic susceptibility and/or lifestyle between Saudi and Swiss women has a considerable impact on the risk of low-grade BC.

Al-Tamimi et al. [30] used gene expression profiling by quantitative real time polymerase chain reaction (qRT-PCR) to identify “intrinsic” subtypes in a Saudi population of BCs and compared the distribution of subtypes to the more commonly profiled Caucasian population. In addition, the Immunohistochemical profile of BC was correlated to the gene expression analysis. Frequency of HER2+ subtype in the Saudi cases was high (28%) by both the procedures of classification. Triple-negative tumors comprised 39%, while only 11% showed a basal-like profile.

In a Saudi population based study on protein expression profile and prevalence pattern of the molecular classes at one of the universities in Dammam, Al-Tamimi et al. [31] analyzed the spectrum of molecular subtypes using ER, PR, HER2, EGFR and CK5/6 as surrogate markers for gene expression profiling to classify the 231 BC specimens. The correlation of each molecular class with Ki-67 proliferation index, p53 mutation status, histologic type and grade of the tumor was also performed. Results of the study demonstrated a prevalence pattern that is unique to Saudi population; luminal tumors (19.9%) and the unclassified group (penta negative, 42.8%), a distribution which is specific to Saudi population and is in contrast with the Western studies.

Knowledge of BC and Practice of BSE: Breast cancer is one of the leading causes of death among cancer patients. Literature reports show that the beginning of screening programs has significantly checked the incidence of this dreadful disease [32]. However, the knowledge of BC and BSE is to be ascertained before corrective measures are taken up. Following is a brief revelation of the knowledge on awareness of BC, BSE and mammography among different sections of the society including general population, doctors, teachers, nurses, students.

Men’s Knowledge: Awareness of BC knowledge and attitude of men in general and husbands in particular on BSE and mammography are to be seriously considered. In a study on 550 participants in Jeddah, Al-Amoudi and Abduljabbar [33] found about 24% of the participants did not know the symptoms of BC. Only about 57.6% were aware of the importance of BSE in early detection and approximately 90% had no idea of the importance of mammography.

Womens’ Knowledge: In an analysis of women’s knowledge and attitude toward BC, Saudi women (500) were interviewed in Dammam on their awareness towards various aspects of BC. Education was the only examined factor that correlated with interviewees’ awareness and attitude. Individuals with university or higher education were more knowledgeable than uneducated or those with only primary schooling or those who had intermediate or high school education. The authors concluded that academic education alone is not enough to adopt the recommended health behaviors. Primary care physicians and community cancer centers have to work jointly for establishing cancer health education or prevention and early detection programs [34]. Saudi women (157) were
randomly interviewed in Jeddah by questionnaire to find out knowledge and practice of BSE and attitude towards BC. Eighty (51%) were illiterate. 19 (12%) were found to conduct BSE, Majority (92%) showed willingness to seek medical advice on discovering lumps in their breasts. Early detection of BC, prevention and cure was the motive. A considerable number of individuals were unwilling to seek medical advice out of fear of cancer and shyness [35].

To assess knowledge and attitude of Saudi females towards screening mammography, a sample of 400 Saudi females were interviewed using a structured questionnaire in Dammam. The results showed poor knowledge and attitude among 41.8% of the participants in relation to not having mammography done or not wishing to have it done, 12.8% who had not had mammography done, but wished to have it, 16.8% wished to have it done every one to two years. The study showed that there has been deficient knowledge and attitude towards screening mammography even among the highly educated [36].

Three hundred women in Qassim were investigated on their awareness regarding BC and BSE. The outcome of the study revealed that the level of awareness was not satisfactory, despite of the fact that majority of them were literate [37]. The knowledge of risk factors was also less. Nearly 26% had no idea of presenting the symptoms of BC and approximately 70% had never heard of BSE, while there was a positive attitude to learn. Majority (74%) of the respondents did not have access to breast health information.

Alam [38] conducted a study (864 respondents) in Riyadh to assess knowledge of BC and sources of information about BC and BSE. The outcome of this study revealed that the level of awareness was not satisfactory, despite of the fact that majority of them were literate [37]. The knowledge of risk factors was also less. Nearly 26% had no idea of presenting the symptoms of BC and approximately 70% had never heard of BSE, while there was a positive attitude to learn. Majority (74%) of the respondents did not have access to breast health information.

Amin et al. [39] reported knowledge deficits regarding BC risk factors and under-utilization of the recommended BC screening in a study on 1,315 Saudi adult females in Al Hassa. The questionnaire included inquiries regarding knowledge, screening practices including clinical breast examination (CBE), mammography, individual BC risk factors and perceived barriers towards (CBE). The outcome of the study showed the level of knowledge was low and dependent upon educational and occupational status. Eighteen percent cases showed family history among first and second degree relations and 2% had history of benign breast lesions.

Ravichandran et al. [40] examined self-reported knowledge, attitude and preventive practical on BC in a population of 719 female respondents in Riyadh. Among them 23.1% reported to practice BSE, 14.2% and 8.1% respectively had clinical breast examination (CBE) and mammography. However, 10.0 and 16.1% of the females (40 years and older) reported having had mammography and CBE. The BSE performers were more educated, knew someone with cancer and had heard of cancer warning signals.

Studies were conducted in outpatient clinics in Jeddah to identify men's knowledge and attitude towards early detection of BC by Al-Amoudi and Abduljabbar [33] by distribution of questionnaire to 550 participants. The questionnaire included points on demographics, knowledge and its source on BC, beliefs and practice regarding BSE, mammography and difficulties that may prevent women from seeking medical help. Most of the respondents were employees and physicians. Their source of knowledge was internet (40.4%) and media (30.4%). Breast mass was the most common symptom (36.6%), followed by change breast size (26%) and pain (20.2%), while 24% did not know the symptoms of BC. Thirteen percent believed that all cases of BC ended with mastectomy. Only 57.6% were aware of the importance of BSE in early detection of BC and approximately 90% did not know the importance of mammography.

There is need for development of effective strategies on public awareness and the availability of genetic testing for BC. In a study on awareness and attitude towards women’s interest on BC genes, 599 women in Al-Hassa, showed high interest in genetic testing for BC risk. Their interest reveals insufficient information regarding BC genetic testing and its role in risk analysis [41].

**Doctors:** About 500 doctors of Jeddah and Abha regions were served a questionnaire to know their perception of their roles in education of clinical breast examination and mammogram examination. The results of 337 questionnaires analyzed showed that majority of the health care professionals do not practice clinical breast examination and mammography and their awareness in education is unexpected [42].
Nurses and Nursing College Students: A study on the knowledge and practice of BSE among 149 Saudi female nursing college students in Riyadh revealed 66% students to perform BSE. Majority (62%) of these students reported that they learned the information about BSE in their college curricula. The sample had a very strong belief in nipple discharge as an etiological factor crucial for BC. Studies like these can enhance the knowledge regarding BSE among girls of different schools and colleges [32].

Alsaif [43] conducted a study to investigate the knowledge and practice of BSE among Saudi female nursing college students in Riyadh. A total of 149 students constituted the study. The results indicated that 66% of the sample performs BSE, majority of these learned BSE from their college curricula. The sample showed relevance of nipple discharge as a causing factor of BC.

Yousuf et al. [44] investigated the knowledge of BC and practice of early screening in 210 nurses Jeddah. The results reflected that there is a need to provide continuing nursing education programs for nurses to improve their BC knowledge and practice.

Teachers: In order to increase BC awareness among women, it is imperative to target school teachers to be a source of campaign on knowledge of cancer symptoms, risk factors, attitude towards BSE, mammography and common misconceptions. A survey was conducted on BC awareness among school teachers in Alkhobar. This was a BC campaign designed with lectures and workshops and delivered to school teachers in seven sessions (each attended by 100-150 female teachers). Pre and post workshop questionnaires distributed to assess knowledge of cancer symptoms, risk factors, attitudes towards BSE, mammography and common misconceptions demonstrated minimal basic background knowledge on BC, methods of conducting BSE and the need for mammography. The pre workshop questionnaires showed majority (81%) did not think any of these modalities were necessary. Post workshop questionnaire demonstrated, 45% agreed to perform BSE, 45% agreed to the need of mammographic screening [45].

Teachers (376) working in girl schools in Buraida were investigated to assess BC knowledge about risk factors, their attitudes and factors associated with the practice of BSE. The results of the study showed more than half of the women to have limited knowledge level. Among the respondents, the most frequently reported risk factors were non-breast feeding and the use of female sex hormones as the possible etiological factors [46].

Students (Secondary, High School and College): The effect of school health education program on the knowledge of BC and BSE was investigated in 7663 secondary school students in Jeddah. The outcome of the program was found successful in raising the awareness of secondary school girls and in helping them to practice BSE more effectively [47]. In a study on knowledge of BC and attitude towards BSE, Milaat [48] evaluated 6380 female secondary-school students (mean age = 18.1 years) by questionnaire in Jeddah. It was found that majority (80%) of the students were not able to answer the questions. However, a higher knowledge level was observed in older age, marriage and those having children or had a family history of BC.

A study to assess the BC knowledge level of Saudi female high school and college students was organized in Jeddah by serving detailed questionnaire on BC to 500 students. The results obtained from 337 questionnaires showed the students to be enthusiastic to learn about BC and its prevention, however the level of knowledge on BC among these young females was found very poor [49].

Etiological Factors: Literature reports suggest the following as the possible etiological factors; influence of age, pregnancy, breast feeding, menopausal status, dietary fat, diabetes and obesity, estrogens and progesterons, drugs and antibiotics, genes and their mutations as risk factor [9, 12, 50-56].

Influence of Age on BC: In a review of 5000 histologically confirmed malignancies observed in Riyadh, Koriech and Kuhaymi, [12] reported BC as the most frequent malignancy in females, accounting for 24% of all female cancers, in spite of the infrequency of the traditional risk factors of nulliparity, late age of first pregnancy, late age of menopause, and high dietary fat consumption. Two-thirds of patients with BC were premenopausal. BC in young patients is often associated with a poorer prognosis. Elkum et al. [57] investigated a total of 867 BC patients in Riyadh between 1986 and 2002. The results on clinicopathological characteristics and treatment outcomes compared between younger and older age groups showed young age (< or = 40) to be an independent risk factor for relapse in operable BC patients.

Breast Cancer in young Saudi women is a critical problem. According to the annual report of Saudi National Cancer Registry [58], BCs that developed before 40 years of age constituted 26.4% of all female BCs comparing to 6.5% in the USA. BC in these women is often associated
with a poorer prognosis, however; there has been a paucity of published data in the Middle East population [57]. In a report from Arab countries, Saadat, [25] found that the occurrence of BC is almost 10 year younger than in USA and European countries. The median age at presentation is 48-52 and 50% of all cases are below the age of 50.

A comprehensive literature review of reports of BC in Arab countries was performed. Published articles were identified from different Arab countries, including; KSA, Bahrain, Qatar, Kuwait, Emirate, Oman, Yemen, Iraq, Syria, Jordan, Lebanon, Egypt, Libya, Algeria, Tunisia, Morocco and Sudan. It was found that the average age at presentation of BC in these countries was found a decade earlier than in western countries. This revelation embarks on implications for screening and cancer management strategies, including; the age at which to start screening. Moreover, it will be useless to adopt Western guidelines to plan BC programs [59].

In a study on breast biopsy reports of a mass or lump from 1035 patients observed between January 2001 and December 2010 in Riyadh, Al-Rikabi and Husain [27] found malignancy in both men and female patients. An age wise incidence observed was 18% in patients younger than 40 years and 63.2% in patients older than 60 years. The mean age of onset for malignancy was 48.6 years. The annual rate of incidence of BC in 2001 was 23.5% and 47.2% in 2007 recording an increase of 4.8%. A comparison with the Western Countries showed that the incidence among Saudis is more in the earlier age groups. Rudat et al. [28] also confirmed different age structures of the KSA and American population in an analysis of medical records of 262 female patients with confirmed diagnosis of invasive BC in Riyadh, between 2004 and 2011 and comparing them to published American data derived from the SEER database. The authors suggested that BC in KSA is diagnosed at a much higher stage compared to the United States. Furthermore, Rudat et al., [60] showed no influence of age (40 years or younger) on any adverse impact on survival of BC patients in molecular tumor type (luminal A versus luminal B, Her2neu overexpression, or triple negative) and lymphovascular status (LVO versus LV1). However, age and T stage (Tis, T0-2 versus T3-4) remained statistically significant.

Based on several studies on data from specialized centres, BC was found the most common female cancer in Alkhobar, however, Anim et al., [61] reported a very low hospital case incidence. The disease appeared to be more common in a younger age group, with a higher occurrence of medullary carcinoma compared with studies carried out elsewhere.

**Pregnancy:** Ezzat et al. [50] investigated 28 women with diagnosis of BC during pregnancy in Riyadh. 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 authors concluded that pregnancy does not appear to be an adverse prognostic factor for BC. Khairy and Al-Abdulkarim [62] reviewed the medical records of 220 patients in Riyadh over a period of five years to study incidents of BCs during pregnancy. They studied the tumor characteristics, maternal details, type of treatment delivered and disease outcome and concluded that pregnancy may not be considered an etiological factor for BC.

**Breast Feeding:** In a study conducted during 1982 to 1987 on1658 Saudi nationals suffering from different malignancies in Eastern province, al-Idrissi [9] showed only 4.1% had BC. Majority of the patients were between 31-50 years of age. All the patients were married, multiparous and had breast fed their new born. This study suggests that the incidence of BC among Saudi women was low during 80s. Ductal carcinoma remained the commonest histological type of breast tumor. Multiparous and breast feeding do not give any protection to the patients.

**Menopausal Status:** Al-Idrissi et al. [51] analyzed data on 130 women with invasive BC, seen in Dammam, between April 1981 and November 1990. The objective was to assess the influence of age and menstrual status on the pattern and prognosis of their disease. The authors concluded that in a low risk population, neither age nor menopausal status had a significant influence on survival.

**Dietary Fat:** A case-control study was conducted on 499 women with BC attending an Epidemiology and Scientific Computing Nutrition Researching Riyadh during 1996-2002. Serum levels of triglycerides and total cholesterol were measured. The results showed a significant positive association between risk of BC and intake of fats, protein and calories [52].
**Diabetes and Obesity:** In an attempt to discuss common etiological and predisposing factors like hyperinsulinemia and obesity, Arif *et al.* [53] found that diabetic female patients at a younger age in population from Hail (a city in the northern region of the Kingdom) are susceptible to developing BC. The bases were regional distribution and possible correlation of diabetes and cancer, in addition of the etiological and predisposing factors for both the diseases.

Alokail *et al.* [63] investigated a total of 101 subjects in Riyadh for serum levels of IL-6, TNF-alpha, C reactive protein, leptin, TGF-alpha, adiponectin and insulin in obese and diabetic premenopausal patients and found that effect on adipocytokines and inflammatory mediators contribute to increased BC risk in premenopausal women.

**Estrogens and Progesterones:** Literature reports suggest that estrogens are significant to stimulate the growth of a major proportion of BC. Progesterone plays an important role in breast development and tumorigenesis. The c-erbB2 gene (Her-2/neu) is a proto-oncogene expressed in 10-34% BCs. Hussein *et al.* [54] analyzed the alterations of estrogen and progesterone receptors and Her-2/neu oncogene protein expression in ductal carcinomas of the breast. About 100 mastectomy specimens were examined in Assir, Abha. The results substantiate the point that BC progression is associated with alterations of ER, PgR and HER-2/neu expression.

In a study on 1215 women, enrolled between September 2007 and April 2008 in the first national public BC screening program in Riyadh, found no correlation between afore mentioned risk factors and imaging score of cancer diagnosis.

**Drugs and Antibiotics:** Close association between inherited or functional deficiency of protein C and S and warfarin therapy is frequently reported, however; the association of this therapy with necrosis of the breast is rare complication. Khalid, [55] reported a case of warfarin-induced necrosis of the left breast mimicking inflammatory cancer at a private hospital in Riyadh. Breast fibroadenomas are reported the most common solid lesions found in young women. Alkhuanaizi *et al.* [64] reported four patients in Dhahran, who developed bilateral fibroadenomas, while on cyclosporine therapy following renal transplantation. One patient developed symptomatic giant fibroadenomas and underwent bilateral mammoplasty. While switching to tacrolimus was found to significantly decrease in the size of the breasts in three patients. There are conflicting reports in the literature on the association between antibiotic exposure and BC risk. In a study to assess this association, Tamim *et al.* [65] found a dose-dependent increase in BC risk in association with an antibiotic exposure up to 15 years.

**Genes and Their Mutations as a Risk Factor:** DNA samples from 29 Arab women and 11 Asian women with unilateral BC were investigated for BRCA1 and BRCA2 mutations in Al-Khobar, during 2000 to 2001. The results of the study revealed that BRCA 1 and BRCA2 mutations are likely risk factors to contribute to the pathogenesis of familial BC in patients [56]. Diet play a significant role in DNA methylation, synthesis and repair and intake has been associated with BC. The folate-metabolizing enzyme, methylene tetra hydrofolatereductase (MTHFR) is polymorphic at nucleotides 677 (C→T) and results in allezymes with changed activity and is believed to cause differences in cancer risk susceptibility. The polymorphism and its effect on the food intake and BC risk association were investigated in 100 BC cases in Riyadh. Results of this study suggest that the MTHFR C677T polymorphism may modify the association between dietary intake and BC risk [66]. It has been hypothesized that single nucleotide polymorphisms in genes (p21 or bcl2) increase susceptibility to BC, however; it has not been experimentally proved. Alshatwi *et al.* [67] in a study on the role of genes on BC risk at the same hospital, found reverse mutation TC and Bcl2 genotypes are marginally associated with BC risk, while p21 is not. Furthermore the authors reported that the alleles of Bcl2 are significantly associated with BC risk.

**METASTASES AND RATE OF SURVIVAL**

Most of the common sites of metastases from BC include the liver, lung, bone and the brain, however, metastases to the gastrointestinal tract are rare with patients presenting with small-bowel perforation, intestinal obstruction and gastrointestinal bleeding. Al-Qahtani [4] reported a rare case of a Saudi female presenting with invasive lobular carcinoma and ileo-cecal junction metastasis from BC in Abha.

Ezzat *et al.* [16] conducted an exhaustive study on BC during a 15 year period (1975 to 1991) in Riyadh. In their study a total of 1584 patients were divided into metastatic and non-metastatic groups at the time of their referral. Early BC (Stages I, II) represented 36%, while 64% presented with advanced or metastatic disease.
(Stages III, IV). The majority of patients were premenopausal (64%). Mastectomy was performed in patients with states I-III (1005) in 85% and lymph node dissection in 93%. Only 30% had no pathologic lymph node involvement and in 49% of the patients, lymph node dissection was adequate. Estrogen and progesterone receptors were known in 30% of the patients. At 15 years, the relapse-free survival in Stages I, II and III was 33%, 36% and 18% and the overall survival was 80%, 64% and 45%, respectively. BC in this population affects younger patients (premenopausal) and a higher proportion present with metastatic or locally advanced disease. In an attempt to study the survival rate for all cases of invasive BC, Ravichandran et al. [3] conducted a study to determine 5-year survival in 316 patients in Riyadh. The 5-year survival for duct carcinomas (62.8%) was greater than for adenocarcinomas (55.6%) and lobular carcinomas (50.0%).

**CONCLUSION**

The views of experts from KSA included an amalgamation of a variety of articles published on different facets (epidemiology, knowledge of BC and BSE, etiological factors, metastasis and rate of survival) of BC during last more than thirty years from different research and teaching institutions. It has covered the published work from the different geographical regions of the Kingdom. A total of 80 studies are published, comparison between the different regions of the Kingdom, showed; Central region > Eastern region > Western region > Southern region > Northern region. There are many areas of Kingdom which are not represented in the literature, which shows a drift of patients to affluent regions with better infrastructure and more facilities. It points towards a need to limit unequal progress in the Kingdom. Further studies are warranted to enrich the information for planning of screening, management and preventive strategies of BC in KSA, which may indirectly benefit worldwide health care.

**REFERENCES**


