Recent Studies & Advances in Breast Cancer

Chapter 4

Breast Cancer in Saudi Arabia and its Possible Risk Factors and Control

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Abstract

Breast cancer is the commonest females' cancer and the leading cause of cancer death worldwide. There have been several factors implicated to the etiology of breast cancer, which differ for different geographical locations. The aim of this review was to discuss the most important etiological factors available in the literature with its possible association in the Kingdom of Saudi Araba (KSA). A number of etiological factors have been involved in the etiology of breast cancer. These factors act independently or together to cause breast cancer. The etiological factors discussed in this review include: age factors, age at first birth, early menarche, gender, dietary factors, tobacco smoking, alcohol consumption, low-dose irradiation, obesity, physical activity, lactation, hormonal factors, hormone replacement therapy, steroid hormone receptors, mammographic density, benign breast disease, and genetic factors. This in addition to the role of Her-2/Neu Antigen and triple negative breast cancer (Tnbc). These factors were discussed in view of the existing literature in general and in KSA in particular, in association with the future scope of the prospective research orientations. Such review can provide necessary information to identify individuals at high risk for prevention, early detection, identifying gaps for future research, and appropriate subsequent management, as well as, caregivers' coordination. The ultimate benefit will be a future dramatic decline in the morbidity and mortality of the breast cancer in KSA.

1. Introduction

Breast cancer is the second most prevalent cancer worldwide and, by far, the utmost common females' cancer with about 1.67 million new cancer cases (25% of all cancers) diagnosed in 2012 [1]. Incidence rates of breast cancer vary almost four-fold across the world's different regions [2]. Prevention of new cancer cases from beginning, researchers investigate the risk factors and protective factors. Some risk factors for breast cancer can be escaped, but many are un-avoidable.

Several studies have well-established the relationship between breast cancer and etiological factors including; age factors [3], age at first birth [4], early menarche [5], gender [6], dietary factors [7], tobacco smoking [8], alcohol consumption [9], low-dose irradiation [10], obesity [11], physical activity, lactation [4], hormonal factors, hormone replacement therapy [12], steroid hormone receptors [13], mammographic density [14], benign breast disease [15], and genetic factors [16]. This in addition to the role of Her-2/Neu Antigen [17] and triple negative breast cancer (Tnbc) [18].

However, it is still uncertain, which of the risk factors has the most effective role over others, in the carcinogenesis of the breast cancer. Here, we reviewed linkage studies that have established evidenced based breast cancer risk factors and what was already published in that regard from KSA. Our stress will be on the strengths of a particular risk factors and its potential to yield substantially contribution to the etiology of breast cancer in KSA.

2. Epidemiology

Females' breast cancer incidence rates are tremendously increasing in Arab countries in recent years, and a sensible number of cases are still being diagnosed at advanced stages of the disease [19]. An epidemiological records associated with breast cancer cases diagnosed from 2001 to 2008 among Saudi women indicated that, 6,922 females with breast cancer were registered in the Saudi Cancer Registry. The highest prevalence was found in eastern region of KSA, representing 0.266 per 1000 women followed by Riyadh, and Makkah, constituting 0.205, 0.194, respectively [20].

In 2009 breast cancer accounting for 25.1% of all newly diagnosed female cancers and the median age at diagnosis was 48 years. The age-standardized incidence rate (ASR) for females was 19.2/100,000 and the median age at diagnosis was 47 years. Breast cancer constituted 27.4% of all newly diagnosed female cancers in the year 2010. The average age at the diagnosis was 48; weighted average was 49.8, and range 43-52. The ASR was 24.9/100,000 in 2010 representing an increase in 2010 compared to 2009 [21].

There view described the cases ofbreast cancer among Saudi females during the period from January 1990 to December 2014, indicated that the number of cases is ascendingly increasing. In 2008 there were 1152 cases of females breast cancer compared to 1308, and 1473 in 2009 and 2010 in this order. The proportion distributions of breast cancer was 40.2, 38.7 and 41.2 in 2008, 2009 and 2010, respectively with minorchanges of 33.5, 33.9, and 36.1 at the age group 45-59 [21].

3. Gender

Globally, female breast cancer incidence have been largely described compared to slightly male breast cancer incidence rates. The highest male's incidence rate was reported from Israel at 1.24 per 100,000 man-years, and the highest female's incidence rate was reported from the United States at 90.7 per 100,000 woman-years [22]. In study from KSA that reviewed 1005 breast cancer cases, 2.3% were found to be males [23]. Another study investigated 87 specimens obtained from males, (90.6%) were benign and 9 (9.4%) were malignant [24]. So the prevalence of male's breast cancer in KSA is relatively lower compared to international figures. Furthermore, no study from KSA has related the cause of male's breast cancer to specific etiologic factor.

4. Age Factors

It was well established that the chance of cancer occurrence increase with the increase with age in general [25], and breast cancer in particular [26]. The prevalence of multiple cancer risk factors is high at midlife and incidence rates start to increase for various cancer types [25]. The alarm in this perspective is the increasing incidence of cancer among younger age groups. In KSA, there is a significant increase in the incidence of breast cancer, which happens at an earlier age than in western countries [27]. The average age at the diagnosis of breast cancer was 48 years; weighted average was 49.8, and range 43-52 [21]. Several factors may be hypothesized for the elevated breast cancer among younger Saudi women including; prolonged light exposure at night time, obesity, reduced physical activities, increased awareness programs with availability of early detection. Habitual night sleep shortage, which associated with the lack of melatonin are prevalent in KSA [28]. Melatonin is a small, highly conserved indole with diverse utilities comprise; circadian rhythm regulation, sleep, and cancer inhibition. Melatonin has the ability to detoxification of the free radicals, is a major function for protecting critical molecules (such as DNA) from the destructive effects of oxidative stress, there by preventing cancer. A recent study found that melatonin is effective against breast cancer stem cells inhibiting the cell viability through octamer-binding transcription factor 4 (OCT 4) also known as POU5F1 gene. Consequently, melatonin has a high potential to be used as a treatment for breast cancer [29].

5. Age at First Birth

This entry provides the mean (average) age of mothers at the birth of their first child. It was strongly proven that women having their first birth before the age of 18 years old have only about one-third the breast cancer risk of those whose first birth after the age of 35 years. These facts explains the earlier detected reverse link between overall parity and breast cancer risk, since women having their first birth earlier tend to become eventually of high parity. The influence of age at first birth in reducing breast cancer risk involves testing of varieties of etiological hypotheses [30].

There is a lack of literature from KSA regarding the relationship between age at first birth and risk of breast cancer. In study included 786 Saudi women, the mean age at the birth of the first child was 21.13±3.68 [31]. Another documented indicated that in KSA men get married at age 27, while women get married at age 25 (age at first marriage only) [32]. These facts may indicate a relatively delayed age at first birth with might increase the risk of breast cancer. Therefore, this factor is common in KSA.

6. Early Menarche and Late Menopause

Menarche and menopause denote the start and end, correspondingly, of reproduction age, and both affect breast cancer risk. In a meta-analysis included 118 964 women with breast cancer were gathered from 117 epidemiological studies, the risk of breast cancer was found to increase by a factor of 1•050; p<0•0001) for every single year earlier at menarche, and independently by a lesser amount (1•029; p<0•0001), for each year older at menopause [33]. It was anticipated that excess obesity and high meat consumption are the possible causative factors leading to the decreasing age of puberty [34]. These factors are common in KSA.

A recent study from KSA evaluated the present age at menarche of young girls and examined its link to that of mother's age at menarche. The mean menarche age for the mothers (12.97 ± 1.71 years) was significantly higher than the daughters (11.5 ± 1.48 years). Moreover, a significant positive correlation was detected between mother's age at menarche and daughter's age at menarche (r=0.264, P=0.023) [35]. Although, the mechanisms underlying this association are not well understood, but may be due to elevated levels of estrogen both earlier [36] and later [37] in life in girls with earlier menarche.

7. Dietary Factors

The role of certain dietary factors in breast cancer causality is not totally determined. Several studies do not support the concept that fat intake in middle life has a strong association with breast cancer risk. However, weight gain in middle life contributes considerably to breast cancer risk [38]. On the other hand, strong evidence is existing that breast cancer risk can be

reduced by escaping weight gain and limiting alcohol consumption throughout adult life.

There is a strong evidence that breast cancer risk is influenced by dietary factors. Blood lipid and lipoprotein levels are also influenced by environmental factors and are linked to breast cancer risk [39].

Decreasing of animal protein and increasing of vegetable intake before puberty, may lower peak height growth velocity, proposing a mechanism for vegetable intakes to protect against breast cancer. Based on dietary data, a significant reduction in peak height growth velocity for girls who increases vegetable intakes and decreases animal protein intakes at ages 3 to 5 years which, would delay menarche [40,41].

There is a lack of literature from KSA regarding the relationship between dietary intakes. A study examined the association between dietary fat and breast cancer in KSA, found a significant positive association breast cancer risk and eating of fats, protein and calories [42]. In KSA, the intakes of high protein and caloric food is common all over the country. The main meal for the great majority of Saudi is meat with rise. The intake of fast food in tremendously growing in recent years. This in addition to the comprehensive dairy products consumption. Dairy products include a miscellaneous group of food in terms of the factors that might possibly influence risk. Dairy foods, such as whole milk and various types of cheese, have a relatively higher saturated fat contents, which may increase breast cancer risk. Moreover, milk products may enclose contaminants such as pesticides, which have carcinogenic potential, and growth factors such as insulin like growth factor I, which have been found to stimulate breast cancer cell growth [43].

Difference in the levels of consumption dairy product greatly vary among populations and with the absence of standard method, many studies have very sensibly made assessments based on quantities of consumption within their specific population. Average intake differs substantially amongst different populations such that a level of consumption that is ascertained "high" in one population might be ascertained "low" in another population. Such evidences, however, should be considered in the future prospects of factors influencing breast cancer risk in KSA.

7.1. Tobacco smoking

The epidemiological evidence on the role of tobacco smoking in breast cancer risk was reliable, sustainable literature supports the association between smoking and breast cancer [44]. This association is mainly perceived in women who smoke for anelongated duration, or who smoke for a long time preceding their first pregnancy [45]. It is difficult to assess the burden of smoking among Saudi females, since tobacco smoking is considered as social stigma usually practiced in hide among females [46,47]. Therefore, the reported figures from KSA are

very low. Consequently, it is difficult to assess this factor at present among Saudi population.

7.2. Alcohol consumption

The International Agency for Research on Cancer (IARC) categorizes alcoholic beverages as carcinogenic to humans; alcohol consumption causes several cancers including breast cancer [48]. Alcohol is a well-established risk factor for breast cancer, and public health advice to women is to limit alcohol consumption [49,50].

A prevalence of 7.5% of alcoholic beverages consumption was reported from Northern KSA [51]. Alcohol usage among Saudi is also considered as social stigma more than the case in tobacco smoking. This in addition to the fact that it is completely prohibited by law.

7.3. Low-Dose Irradiation

While high-dose ionizing radiation is associated with amplified breast cancer risks, the link with protracted low-dose-rate exposures left overs blurred. The US Radiologic Technologist study offers an opportunity to study the association between breast cancer incidence and-low to moderate dose radiation. Occupational radiation to the breast was positively associated with breast cancer risk. The risk was more notice able for women born before 1930 who started working before 1950 when mean annual doses (37 mGy) were substantially higher than in later years (1.3 mGy). Because of the doubts and possible systematic miscalculations in the occupational dose estimations before 1960, these outcomes should be dealt with caution [52]. However, we did not come across any study in this regard from KSA.

7.4. Obesity

Overweight and obesity, a global problem, affects more than one billion individuals [53]. Obesity has been linked to various health disorders, including breast cancer [54]. In the Arab population, the risk of breast cancer was significantly greater among females who were overweight or obese equallyfor pre and post-menopausal (Odd Ratio (OR) =2.73 and OR =2.22 respectively; p < 0.0001). A study from KSA, found 75.8% of the cases of breast cancer had abnormal weight. Obese women show more than 2-fold greater breast cancer risk (OR =2.29) compared to those with normal body mass index [55].

Recent studies from KSA reporting very high obesity's prevalence rates. A study from northern KSA had reported a prevalence rate of 71% for obesity among females [56]. Another study had reported prevalence rates for obesity ranging from 55%-70% from 4 different areas [57]. In our opinion obesity is one of the most affected risk factors that strongly contributes to the etiology of breast cancer in KSA.

7.5. Physical activity

An inverse association between early physical activity and breast cancer risk was proved several studies which, assessed physical activity among those under the age of 20 [58]. The average decrease in breast cancer risk associated with physical activity at all ages groups was 16% for adolescence, 8% for early adulthood, 15% for middle adulthood, and 17% for age 50 and older [59]. Some studies have stated that current physical activity has a stronger outcome than activity far in the past [60].

During the past three decades, the KSA has experienced remarkable lifestyle changes, including physical activity and food intake habits. These quick lifestyle changes have absolutely had a significant negative influence on the health of the community. This lifestyle revolution is believed to be responsible for the epidemic of numerous non-communicable diseases in KSA [61]. A study from KSA has reported a prevalence of 96.1% for physical inactivity level among Saudi adults. There were significantly (p<0.001)) more inactive females (98.1%) than males (93.9%) [62]. However, a recent study from KSA has showed a decrease in the levels of physical inactivity. The study reported prevalence rates of physical inactivity of 66.6%, for males and 72.9% for females [63]. The results of these studies signify the role of physical inactivity as a strong factor that may contribute to the etiology of breast cancer in KSA.

7.6. Breastfeeding

A systematic literature search found that breastfeeding >12 months was associated with reduced risk of breast cancer by 26% [64]. Breastfeeding is inversely associated with inclusive risk of breast cancer. This association may vary in breast cancer subtypes categorized by receptor status, as they may denote various mechanisms of carcinogenesis. Results of a meta-analysis showed a protective effect of ever breastfeeding against breast cancers with hormone receptor-negative, which are more frequent in younger females and commonly have a poorer prognosis than other subtypes of breast cancer [65].

The World Health Organization (WHO) has endorsed limited breastfeeding for 6 months after birth [66]. The existing practice of Saudi infants' feeding is extremely far from compliance with even the most conservative WHO endorsements of limited breastfeeding for 4 to 6 months. A study from KSA showed that bottle feeding was introduced by 1 month of age to 51.4% of children and to 90% by 6 months of age [67]. These findings at least show that high proportions of Saudi mothers practice breastfeeding for short period of time, which may increase the risk of breast cancer.

8. Hormonal Factors and Hormone Replacement Therapy

Estrogen hormones have an extensive impact on both normal development and tum-

origenesis of the breast [68]. The IARC first established that there was adequate evidence that estrogen-only menopausal hormone therapy (MHT) was carcinogenic to humans in 1999 [69]. In a subsequent report published in 2012, IARC also reported that there was sufficient evidence that estrogen plus a progestogen (combined MHT) was carcinogenic [70]. In a study reanalyzed around 90% of the global epidemiological evidence on the relationship between breast cancer risk and hormone replacement therapy (HRT) usage, breast cancer risk was found to increase in women using HRT and increases with increasing duration of use. This effect is lowered after ending of use of HRT usage and has mostly, if not completely, disappeared after about 5 years [71].

Progesterone is a sexual steroid hormone that has a vital role in reproductive processes in males and females. Progesterone has been linked to several disorders such as breast disease, and also involved in regulating cell proliferation, apoptosis, and metastasis. Membrane progesterone receptors (mPRs) mediate the majority of the non-classical progesterone activities. The role of the various mPRs subtypes in progesterone actions in reproduction and cancer is an evolving and motivating research area [72].

There is a paucity of data regarding HRT from KSA, the only one study undertaken this topic in 2003 and reported a prevalence rate of HRT of 5% [73]. A recent study from KSA have reported long term use of oral contraceptive pills (OCP) in KSA and its association with increased breast cancer risk [74]. In the absence epidemiological data regarding the OCP usage among Saudi women, it is difficult to incriminate this factor as contributing to the etiology of breast cancer in KSA.

9. Steroid Hormone Receptors (SHR)

SHR such as estrogen receptors (ERα and ERβ), are found in the nucleus, cytosol, and on the plasma membrane of target cells. They initiate signal transduction for steroid hormones, which leads to alterations in gene expression [75].

Steroid receptor RNA activator (SRA) is a type of long noncoding RNA (lncRNA) which synchronizes the functions of different transcription factors, improves steroid receptor-dependent gene expression, and also works as a discrete scaffold. SRA can activate androgen receptor (AR), ERα, ERβ, progesterone receptor (PR), and glucocorticoid receptor (GR). SRA plays a key role in both biological processes, such as, myogenesis, steroidogenesis, and pathological changes, such as obesity and tumorigenesis [76]. Studies found that steroid hormones and their nuclear receptors play a key role in the growth and progression of breast cancer [77].

Prevalence of Estrogen and Progesterone Receptor expression in breast cancer in the Saudi population is parallel to that described globally [78].

10. Metabolic and Secretory Factors (MSFs)

MSFs have both protection and risk which, due to variances in the levels of metaboli-cand secretory activity of the breast. Women of the drycerumen genotype (common among Asians and rare among whites) have lesser levels of secretory activity in the epithelial cells that line the breast ducts than women of the wet cerumen genotype. The difference may decrease risk of breast cancer by protecting the breast ductcells of dry cerumen women from exposure to environmental and dietary carcinogens and cancer promoting substances secreted into breast ducts from plasma [79]. To the best of our knowledge no study has investigated this factor from KSA.

11. Mammographic Density (MD)

MD is a strong risk factor for breast cancer [80]. Dense breast tissue looks light on a mammogram and is consist of of epithelial and stromal tissue while, non-dense tissue, consist of fat, appears dark. Women with over 75 % dense tissue have 4 to 6 times breast cancer risk compared to those with very little to no dense tissue [81]. However, it is indistinct whether high MD is an intermediate phenotype or whether the risk factors of breast cancer affect breast cancer risk and MD independently [82].

Studies from KSA in this context have dealt with Mammography as screening tool rather than reporting epidemiological figures about the MD. Therefore, this risk factor need more research to provide sufficient data for suitable correlation measurement.

12. Benign Breast Disease (BBD)

BBD is a strong later breast cancer risk factor, which can grow in either breast [83]. It involves a variety of histologic pattern, commonly divided into non-proliferative lesions, proliferative lesions without atypia, and atypical hyperplasia, with an elevated risk of breast cancer associated with proliferative or atypical lesions [84].

In study evaluated the profile of female breast lesions in KSA, BBD contained 55.24% of all lesions (mean age 31.7), the most frequently reported being; fibroadenoma 46.9%, fibrocystic disease 23.25% and fibroadenosis 14.5% [85]. Out of 1005 breast biopsies obtained from Saudi, 603 cases (60%) were found with BBD [86]. Out of 969 records reviewed in KSA, BBD accounted for 60.1%. Multiple BBDs were found in 51.1% and more than two lesions in 21.1% of the cases. Non-proliferative BBD with low risk were identified in 81.4%, intermediate risk lesion without hyperplastic atypia were found in 14.6%, where as high risk lesions with atypia were revealed in 4.0% [87]. Another study from KSA have reported a prevalence of 35% of NND [88].

13. Genetic Factors

About 5% to 21.5% of breast cancers arise from germ-line mutations associated genes such as BRCA1, BRCA2, p53 and PTEN, which render an individual at risk for developing hereditary breast cancer [89, 90]. The BRCA1 and BRCA2 genes are located on the long arm of chromosomes 17 and 13, respectively. Patients with positive gene expression have approximately 80% risk of subsequent development of breast cancer mainly around pre-menopausal age [91].

Most of the data from KSA searched for irregularly hereditary mutations rather than to screen for these hereditary mutations to provide epidemiologic data for Saudi population. One study in this context, however, has determined whether any correlation present between single nucleotide polymorphisms in breast cancer associated BRCA1 and breast cancer associated BRCA2 and breast cancer risk. The study showed that neither BRCA1 nor the BRCA2 studied variant illustrate any significant association with the breast cancer among Saudi women [92]. Therefore, this factor needs more research to determine whether it has a significant role in the etiology of breast cancer in KSA.

14. The Role of Her-2/Neu Antigen

Human epidermal growth factor receptor 2 (HER2) is a member of the human epidermal growth factor receptor family. Amplification of this oncogene has been revealed to play an essential role in the development of definite aggressive types of breast cancer [93]. Neu is so named because it was derived from a rodent glioblastoma cell line [94]. HER-2/neu proto-oncogene was found to be over-expressed in 20–30% of invasive breast cancers, and it is associated with worse outcome and short survival [95].

A study from KSA, had shown that, Her-2/neu gene amplification by fluorescent in situ hybridization was noticed in 84.6% of breast cancer that were 3+ and in 18.75 % cases that were 2+ by immunohistochemistry. There is a negative association between hormonereceptors expression and Her-2/neu amplification. Nevertheless not all of the high-grade breast cancers revealed Her-2/neu positive status [78]. Another study from KSA, reported that HER-2/neu oncogene was amplified in approximately 18% of invasive ductal carcinoma of the breast and is associated with poor prognosis [96]. The findings of these study may signify the role of HER2/neu in the breast cancer among Saudi women.

15. Triple Negative Breast Cancer (Tnbc)

TNBC denotes breast cancer patients with negative ER, PR and HER-2/neu receptors [97]. Compared to other breastcancer subtypes, TNBC is more aggressive, and more commonly affects younger patients [98]. TNBC represent about 15%-25% of all breast cancer

cases [99]. Epidemiologic studies strongly support that TNBCs may be distinct entities as compared with ER+ breast cancer, suggesting that the etiologic factors, clinical characteristics, and therapeutic options may differ by molecular subtypes. Many studies propose that reproductive factors and exogenous hormone usage differently or even quite inversely influence the risk of TNBCs and ER+ breast cancers. Arguments regarding the exact role of even the same risk factor in TNBC growth explain that the biological process behind the initiation of both TNBCs and non-TNBCs are entirelyunclear [100].

A recent study from KSA has reported a prevalence of 14.8% for TNBC [101]. However, should be considered in the future research to verify its role in the etiology of breast cancer in KSA.

16. Control and preventive measures

The Collaborative Group on Hormonal Factors in Breast Cancer (2002) estimated that the cumulative incidence of breast cancer in developed countries would be reduced by more than half, from 6.3 to 2.7 per 100 women, by age 70 if women had on average more children and breastfed for longer periods as seen in some developing countries [102]. Given global increases in population growth and the strong evidence that a woman's ability to control her fertility may improve her social, economic, and overall health, it is not considered desirable to increase the birth rate per woman or to encourage pregnancies at a very young age. However, breastfeeding can and should be encouraged for many reasons, including possibly for the reduction of breast cancer risk. Many of the risks of reproductive factors are related to the effects of estrogen as demonstrated by the reduction in breast cancer incidence after an early oophorectomy, by inhibition of the estrogen receptor (ER) by using selective estrogen receptor modulators (SERMs) such as a tamoxifen or raloxifene [103], or by blocking estrogen synthesis by using aromatase inhibitors (AIs) such as exemestane [104] and anastrozole [105,106].

On the other hand the application of measures that are already available, such as chemoprevention and lifestyle prevention, would result in appreciable reductions in breast cancer risk. Another factor is that the pace of advance of our understanding of the biology of breast cancer risk and development is highly likely to give rise to new avenues for prevention over the next 10 years. A major problem is applying what we already know concerning the efficacy of prevention to appropriate populations of women. To apply chemoprevention, we need to have measures in place to assess risk and to explain the pros and cons of treatment and for prescription of appropriate therapies. Lifestyle change is a population problem which involves publicity concerning its risks and benefits of change and providing mechanisms to support women in their choices throughout society [107].

In summary, this review highlighted very important factors that contribute to the etiology of breast cancer in KSA in light of the available evidences and highlighted the possible

gaps that can be addressed in the future. Knowledge of breast cancer risk factors can strongly contribute to the breast cancer prevention efforts, which will have the greatest outcome particularly if initiated at an early age and sustained over a lifetime. Gaps in knowledge are rendered predictable and deserve valuable attention to clarify prevention.

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