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An Assessment of Risk Factors for Breast Cancer Among Women Attending Breast Cancer Screening in Saudi Arabia

By

Saleh Nasser S Alqarni

Degree to be awarded: MPH

Hubert Department of Global Health

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Ghada N. Farhat PhD, MPH
Committee Chair

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M.B.B.S.
King Saud University
2010

Thesis Committee Chair: Ghada N. Farhat, PhD, MPH

An abstract of
A thesis submitted to the Faculty of the Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of Master of Public Health
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ABSTRACT

Background: Breast cancer is the most common malignancy among women worldwide. In Saudi Arabia, the age-adjusted incidence rates for breast cancer have been increasing over time; however, disease etiology remains poorly understood. We performed a secondary data analysis to assess risk factors for breast cancer among Saudi women through analyzing data from the National Breast Cancer Early Detection Program (NBCEDP).

Methods: Data was collected by the NBCEDP between January 2012 and July 2016. During this period, 45,000 women were screened for breast cancer out of which 300 were diagnosed with invasive breast cancer. Our analysis included 8365 screened women (60 confirmed cases and 8305 non-cases) who had data on risk factors collected under a pilot research study conducted by the program. Logistic regression was used to identify associations for breast cancer risk factors with disease risk.

Results: Well-established breast cancer risk factors (such as reproductive factors, personal or family history of breast cancer, overweight or obesity) were not found to vary significantly between cases and non-cases. The only factors to show statistically significant associations with breast cancer risk were level of education (Odds Ratio [OR] for primary, secondary or high school education= 0.13, 95% CI= 0.02 – 0.71; OR for college or postgraduate education= 0.34, 95% CI 0.07 – 1.53, compared to illiteracy) and time spent doing physical activity [hours per week] (OR = 1.03, 95% CI 1.01 – 1.05).

Conclusion: Additional studies using a larger number of cases and employing a longitudinal design are needed to confirm our findings of no association with established risk factors and to further investigate novel risk factors for breast cancer among Saudi women.

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Chapter I. Introduction

Breast cancer is the most common cause of cancer incidence and mortality and the fifth leading cause of total mortality in women worldwide (International Agency for Research on Cancer, 2012). The increasing mortality rate is a public health concern given that around 571,000 people died from this disease in 2015, compared to a relatively lower mortality rate in 2012, with around 521,907 deaths (International Agency for Research on Cancer, 2012). In the United States of America (USA), estimates from the American Cancer Society for 2017 indicate that breast cancer is the leading cause of cancer incidence among women, accounting for 252,710 new cases (30% of all cancers), and the second leading cause of mortality, accounting for about 40,610 cancer deaths (14% of all cancer deaths) (American Cancer Society, 2017a).

In both industrial and non-industrial countries, breast cancer is the highest-ranking cancer in terms of incidence among females; however, there are differences between these countries in terms of age at diagnosis, disease stage at presentation, and biological characteristics of breast cancers. For instance, in the United States, about 50% of newly diagnosed breast cancer cases occur among women older than 63 years of age while in non-industrial countries about the same percentage of newly diagnosed cases occurs among women younger than 50 years (Rodríguez-Cuevas, Macías, Franceschi, & Labastida, 2001). This represents a public health concern, as the diagnosis of disease at an earlier age is correlated with a worse prognosis regardless of menopausal status (Dubsky et al., 2002). Also, the stage of breast cancer at diagnosis differs widely between the two groups of countries, where the patients in non-industrial populations usually seek medical care at an advanced stage of the disease, at the local invasion or metastatic phase, whereas in the industrial countries the disease is detected early by screening and is treated at earlier stages of the disease, including in-situ breast cancer (Li, Daling, & Malone, 2005; Murray, 2003).

The Kingdom of Saudi Arabia (KSA) and other countries in the Arabian Peninsula, are non-industrialized countries (World Economic Situation and Prospects, 2014) that have newly adopted a modern lifestyle similar to that of industrialized countries. Although these countries have lower breast cancer incidence rates than industrialized countries (International Agency for Research on Cancer, 2012), they are witnessing an increasing trend in breast cancer occurrence, and projections indicate that incidence rates will continue to rise (Al-Rikabi & Husain, 2012; E. O. Lee et al., 2004). In fact, currently, the age-adjusted incidence rate among Saudi females has been increasing over a 19-year period, from 13.3 per 100,000 in 1994 to 25.5 per 100,000 in 2013, as estimated by the Saudi Cancer Registry (SCR) (Saudi Cancer Registry, 2016). However, there is no national data about mortality rates of this cancer in KSA.

A major problem of breast cancer in KSA is its late presentation and poor prognostic outcomes. The late presentation of breast cancer patients in Saudi Arabia was found to be due to, in part, the Saudi cultural values, where women tend to ignore symptoms while the disease is aggressively attacking. This conservative nature of the Saudi society (such as fear of cancer, shyness, family restrictions, and fear of social implications) and other reasons including poor health awareness and difficulty in accessing health care were considered barriers for Saudi women to seek breast cancer diagnosis and treatment at earlier stages of the disease (Alam, 2006; Amin, Al Mulhim, & Al Meqihwi, 2009). The common late presentation among Saudi females with breast cancer has created a difficult situation for them and their families, as well their social lives. This is especially true amongst the youngest patients.

By comparison, in USA, a country with well-established and organized cancer prevention programs, the age-adjusted breast cancer death rate has been decreasing from 30.6 per 100,000 population in 1995 to 20.5 per 100,000 population in 2014 (American Cancer Society, 2017b; Smith & Brawley, 2014). This decrease is due to the efforts that have been done so far to raise public health awareness regarding breast cancer and improving the screening process to expand coverage to the majority of the population (Health Resources and Services Administration, n.d.).

KSA aims to lower breast cancer rates and improve prognosis. The Ministry of Health (MoH) and other health stakeholders in KSA are seeking solutions for breast cancer, including the late presentation patterns found in the country. Ongoing assessment of risk factors, mammography screening, and raising public awareness about disease prevention and early detection are established factors to reduce the incidence and mortality of the disease. To this end, the Saudi MoH established the National Breast Cancer Early Detection Program (NBCEDP) in 2012 in the capital city of Riyadh. The NBCEDP provides screening to any woman who seeks its services. Despite such efforts, there are major gaps in the country related to breast cancer knowledge, as well as the translation of knowledge to programs and policies for breast cancer prevention. Therefore, there is an urgent need in KSA to build a knowledge base on breast cancer etiology and to understand the extent to which well-known risk factors for breast cancer apply to Saudi women. To address this need, we conducted a secondary data analysis using population-based data from the only governmental and the largest breast cancer screening program in KSA. Our aim was to perform a comprehensive assessment of risk factors for breast cancer among women in KSA. This research provides valuable information that will help understand and better characterize the risk factor profile for breast cancer among Saudi women. Such information will contribute significantly to the current body of evidence on breast cancer etiology and will set the stage for evidence-based prevention efforts.

Chapter II. Literature Review

Breast Cancer Epidemiology

Breast cancer is the most common cause of cancer incidence and mortality and the fifth leading cause of total mortality in women worldwide (International Agency for Research on Cancer, 2012).

In KSA, breast cancer is the leading cancer in incidence, accounting for 29.1% (6,364 cases) of all cancers in women and men combined. The number of cases of breast cancer has been increasing over the years, with 1,853 cases diagnosed in 2013, in comparison to 1152, 1308, and 1473 cases diagnosed in 2008, 2009, and 2010, respectively (Saggu, Rehman, Abbas, & Ansari, 2015; Saudi Cancer Registry, 2016). Among females, the 2013 age-standardized rate (Albasri) was observed to be 25.5 per 100,000 population (Albasri, 2014). The Eastern region had the highest ASR with 41.0/ 100,000 population, followed by Riyadh with 29.3/ 100,000, Makkah with 25.3/ 100,000, the northern region with 25.0/ 100,000 and Tabuk, with 24.9/ 100,000 population, according to the 2013 statistics (Saudi Cancer Registry, 2016). However, in comparison to other countries around the globe, KSA is still considered to have a low incidence rate, although more women present with advanced disease stages at diagnosis (Alghamdi, Hussain, Alghamdi, & El-Sheemy, 2013; Amin, Al Mulhim, et al., 2009). Unfortunately, there is no breast cancer mortality estimates in the country due to the incomplete infrastructure of cancer surveillance.

Breast Cancer Etiology

Age

Age is a well-established risk factor for many non-communicable diseases, including cancers worldwide. About 25% of new breast cancer cases occur between the ages of 65-74 years (The National Cancer Institute, 2015). In the Arab world, the average age at diagnosis of breast cancer was found to be 48 years, a decade younger than the corresponding estimate in western countries (Najjar & Easson, 2010). In Saudi Arabia, reports from the Saudi Cancer Registry indicate that the median age at diagnosis of breast cancer is 50 year, an estimate that is younger than the median age for women in North America and Western Europe (61 years) (The National Cancer Institute, 2015), where most cases are among postmenopausal women (Saudi Cancer Registry, 2016).

Reproductive History

Reproductive history is another risk factor that is strongly related with breast cancer. It has been observed that an early age of menarche (before 12 years) and a late age of first-time full-time pregnancy (after 30 years) are both related to breast cancer diagnosis after menopause, and even more so in premenopausal women. A prospective cohort study done in France from 1990 to 1997 recruited a sample of 91,260 French female participants between the ages of 40-65 years over two-years (1990 and 1991) who were asked to answer lifestyle questions, including reproductive factors. The age of menarche, age of first full-term pregnancy, overall number of full-term pregnancies and menopausal status were recorded. Out of this large sample, 1,718 breast cancer cases were identified. The study results provided significant evidence that the overall risk of breast cancer increases with earlier age at menarche, later age of first pregnancy, and low parity, all with variation according to menopausal status. Higher age of menarche was shown to decrease the risk of breast cancer by 7% per year (Relative risk [RR]=0.93, 95% Confidence Interval [CI] 0.87 – 0.99) among premenopausal women and by 3% per year (RR=0.97, 95% CI 0.93 – 1.01) among postmenopausal women. The study found that with higher age at first full-term pregnancy, the risk of breast cancer increases by 4% among premenopausal women (RR=1.04, 95% CI 1.02 – 1.06) and by 2% among postmenopausal women (RR=1.02, 95% CI 1.00 – 1.04). Also, the more full-term pregnancies a woman had was observed to have a protective effect amongst postmenopausal women only (RR=0.91, 95% CI 0.86 – 0.96; P<0.001) (Clavel-Chapelon & Group, 2002).

Another study done in the United Kingdom in 2000 found that women who did not have children or who had a late age of first birth (after 30 years of age) had a higher risk for breast cancer than women who have had children or had given birth at an earlier age (before 20 years of age). In fact, the highest risk group are those who gave birth after the age of 35 years (McPherson, Steel, & Dixon, 2000).

In Saudi Arabia, a cross-sectional study done in 2003 found that women have their first child at a mean age of 21 years (Standard Deviation [SD]= 3.68 years) (Abdel-Fattah, Hifnawy, El Said, Moharam, & Mahmoud, 2007). However, this age estimate is likely to increase over time. The General Authority of Statistics in Saudi published a comparison of marriage rates between 1992 and 2010. There has been an increase since 1992 in the percentage of women who became married at an older age, with detailed statistics available. The percentage of women who became married between 20—24 years of age has decreased by 3.25% and by 0.32% among women aged between 25—29 years. On the other hand, there was an increase in the percentage of women who became married among women aged between 30—34 years by 2.17%, by 1.31%

among women aged between 35—39 years, by 1.95% among women aged between 40—44, and by 1.51% among women aged between 45—49 (The Saudi General Authority of Statistics, 2017). This might be an indication of a new pattern for age at first birth in the Saudi society, which might have implications on breast cancer rates.

Breastfeeding

The period of breastfeeding has been recommended by the World Health Organization (WHO) to be no less than 6 months (Kramer & Kakuma, 2012). In a systematic literature review, the risk of developing breast cancer was found to decrease by 26% among women who breastfeed cumulatively for more than 12 months (Chowdhury et al., 2015).

In KSA, there is a study that found about 51.4% of children are started on bottle feeding by the age of 1 month and 90% of children who are at 6 months of age are on bottle breastfeeding (El Mouzan, Al Omar, Al Salloum, Al Herbish, & Qurachi, 2009). Thus, this might indicate that there is a very low rate of breastfeeding amongst Saudi women even below the duration recommended by the WHO (6 months), which is less than the duration reported to result in reduction in breast cancer risk (minimum of 12 months). The relationship of breastfeeding with developing breast cancer in Saudi women needs to be assessed further, especially with the available evidence showing very low breastfeeding rate.

Exogenous Sex Hormones

Postmenopausal hormone therapy (PHT) has been examined in many studies and found to be related to developing breast cancer. The Women's Health Initiative (WHI) clinical trials assessed the effects of PHT, diet modification, and calcium and vitamin D supplements on major health outcomes, including heart disease, fractures, and breast and colorectal cancer in generally healthy postmenopausal women (n= 161,608). The hormone therapy component of the WHI clinical trials assessed the risk of developing breast cancer in relation to two hormone therapy formulations, estrogen and progestin and estrogen-alone. These trials observed that the utilization of estrogen plus progestin therapy, but not estrogen-alone, was significantly associated with developing breast cancer amongst women after menopause with a hazard ratio of 1.24 ($p<0.003$) in comparison with the placebo group (Chlebowski, Hendrix, Langer, & et al., 2003).

The Collaborative Group on Hormonal Factors in Breast Cancer published a meta-analysis of 51 observational epidemiologic studies done in 21 countries, across the world, where they evaluated the effect of PHT using individual data from 52,705 women diagnosed with breast cancer and 108,411 free of the disease. The analysis was done mainly on 53,865 postmenopausal women with a known age of menopause and known usage of PHT at some time in their life (17,830 women, 33%). Relative risk estimates of breast cancer with the usage of PHT were done by a stratification of all analyses by study, age at diagnosis, time since menopause, body mass index, parity, and the age of the woman at the delivery of first child. The relative risk to develop breast cancer among women who never used PHT increased by 1.03 (95% CI=1.02-1.03) for each year increase in the age at menopause. On the other side, the relative risk for women who had used this therapy for five years or more was found to be 1.35 (95% CI=1.21-1.49; $p=0.00001$) compared to women who never used it. Also, those who used PHT between 1 to 4 years showed an increase in relative risk by 1.02 (95% CI=1.01-1.04; $p=0.0002$) with each year of use compared to women who never used it. For those who stopped using PHT for 5 years or more, there was no significant increase in developing breast cancer overall, regardless of the duration of use. Many factors were evaluated with this association, but only the weight of the women and body mass index were found to be significant. Among postmenopausal women, the estimated cumulative excess in breast cancer cases was found to be 2 per 1,000 users of PHT for 5 years (95% CI =1–3), 6 per 1,000 users of PHT for 10 years (95% CI =3-9), and 12 per 1,000 users of PHT for 15 years (95% CI =5-20). However, information on the effects of PHT on mortality from breast cancer were not investigated (The Collaborative Group on Hormonal Factors in Breast Cancer, 1997).

One of the largest studies on PHT was done in the United Kingdom between 1996 and 2001 on women who had no cancer diagnosis before, except for non-melanoma skin cancer. The recruitment was done by invitation of The National Health Service Breast Screening Programme (NHSBSP) to all women in the UK, aged 50-64 years, for routine screening once every 3 years. A follow-up of 1,084,110 UK women, the Million Women Study, provided evidence on the association between developing breast cancer and the use of PHT, by duration of use and type of therapy, in terms of incidence and death. The analyses were stratified by age at recruitment and adjusted for time since menopause, childbearing history, a first-degree relative with a history of breast cancer, body-mass index, region, and five categories of deprivation index. An incidence of 9,364 breast cancer cases and a death total of 637 participants were observed. The overall relative risk of developing the disease among women in this study increased with a higher total duration of PHT use. The relative risk of death from breast cancer increased in women who were active users of PHT at recruitment time (1·22, 95%CI=1·00–1·48), but not in past users (1·05, 95%CI=0·82–1·34) compared to women who never used it (Million Women Study Collaborators, 2003).

Regarding oral contraceptives, there is no consistent evidence in the literature that the history of use, duration of use, age at initiation, or time since discontinuation, is correlated with developing breast cancer among women (Hunter et al., 2010; Marchbanks et al., 2012; Zhu, Lei, Feng, & Wang, 2012).In one study, the starting age of using oral contraceptives was found to be correlated with developing breast cancer among women with BRCA1 gene mutation (Kotsopoulos et al., 2014).

In Saudi Arabia, a minimal number of research studies has been done on PHT and oral contraceptive use in general and in terms of their association with breast cancer. One study done in the west of KSA in the city of Jeddah found the prevalence rate of PHT use to be 5% (Bakarman & Abu Ahmed, 2003).

Endogenous Sex Hormones

Circulating sex hormones have been correlated with breast cancer risk factors and with developing breast cancer among women. In a cross-sectional analysis of more than 6,000 postmenopausal women controls across 13 prospective studies, sex hormones concentrations were strongly associated with several established or suspected risk factors for breast cancer including age, menopause status, body mass index, smoking, alcohol, reproductive factors, and family history of breast cancer which may mediate the effects of these factors on risk of developing breast cancer. Estradiol, calculated free estradiol, oestrone, androstenedione, dehydroepiandrosterone sulphate (DHEAS), testosterone, calculated free testosterone, and sex hormone-binding globulin (SHBG) were significantly associated with age. Estradiol, oestrone, and SHBG did not differ significantly across type of menopause. The aforesaid hormones and SHBG were significantly associated with body mass index. Also, it found that sex hormones concentrations were higher in women who smoked 15 or more cigarettes per day or consumed 20 grams or more alcohol compared to women who never smoked or drunk, respectively. Among all aforesaid hormones, only oestradiol, calculated free oestradiol, and DHEAS were associated with time since menopause (Endogenous Hormones and Breast Cancer Collaborative et al., 2011).

Another study among postmenopausal women found that high serum levels of sex steroids, estrogens and androgens, were associated with increased risk to develop breast cancer after adjusting for potential confounding factors such as body mass index. In this case-control study the odds ratios for the highest versus lowest quartiles of androgens were as follows: DHEAS 1.69 (95% C.I.=1.23-2.33), androstenedione 1.94 (95% C.I.=1.40-2.69), testosterone 1.85 (95% C.I.=1.33-2.57) and free testosterone 2.50 (95% C.I.=1.76-3.55). For the oestrogens, the odds ratios were: oestrone 2.07 (95% C.I.=1.42-3.02), oestradiol 2.28 (95% C.I.=1.61-3.23) and free oestradiol odds ratios of 2.13 (95% C.I.=1.52-2.98). However, SHBG was inversely associated with developing breast cancer (Kaaks et al., 2005). An earlier study to the aforesaid study that had same design with a larger sample size had similar observations in the same directions for the association of androgens and estrogens with developing breast cancer (Zeleniuch-Jacquotte et al., 2004). Another study that investigated levels of endogenous sex hormones among postmenopausal women in a nested case-control study found an increased risk of developing breast cancer among those women who had high levels of estrogens and androgens, but there was no association between developing breast cancer and the serum levels of progesterone or sex hormone binding globulin. In this study, the investigators restricted the analysis to case subjects with estrogen receptor-positive and progesterone receptor-positive (ER+/PR+) to estimate the relative risk of developing breast cancer comparing the highest and the lowest fourths of plasma hormone concentrations where they found that the relative risk of estradiol to be 3.3 (95%C.I.=2.0-5.4), testosterone to be 2.0 (95%C.I.=1.2-3.4), androstenedione to be 2.5 (95%C.I.=1.4-4.3), and dehydroepiandrosterone sulfate to be 2.3 (Missmer, Eliassen, Barbieri, & Hankinson, 2004).

History of Benign Breast Disease

The relation between the risk of developing breast cancer and benign breast diseases has been investigated in few studies. A study published in 2004 that used data from 11,307 women (randomized) from 1992—1997 with no history of atypical hyperplasia or *in situ* breast cancer, obtained through the National Surgical Adjuvant Breast and Bowel Project's Breast Cancer Prevention Trial, found that women with low-category of benign breast disease (LC-BBD) showed a statistically significant higher risk of developing breast cancer (RR=1.60, 95% CI=1.17 -2.19) compared to women with no LC-BBD, especially among women aged 50 years and older (Wang et al., 2004).

Another retrospective cohort study was conducted on women enrolled in a population-based screening program in Spain and found increased risk of breast cancer with proliferative and non-proliferative benign breast disease, regardless of the family history of breast cancer. The sample size included 545,171 women aged 50-69 years, biennially screened for breast cancer, with a 6.1-year median time of follow-up. The analysis estimated the age-adjusted rate ratio of breast cancer for women according to both proliferation categories, with or without atypia, and stratified by family history of breast cancer. The results showed that the age-adjusted rate ratio for developing breast cancer after a woman was diagnosed with benign breast disease was 2.51 (95 % CI: 2.14–2.93) compared to women without benign breast disease. The risk of developing breast cancer was minimal but significantly increased for women with non-proliferative disease (RR = 2.23, 95 % CI: 1.86–2.68) (Castells et al., 2015).

A study published in 2005 followed a sample of 9,087 women with a median age of 15 years to find reliable estimates and relations in regard to benign breast disease developing into breast cancer. Women who were diagnosed with benign breast disease at the Mayo clinic from 1967 to 1991 had their data collected. Their breast cancer diagnoses were collected from medical records and questionnaires to estimate the relative risks. Their findings showed that there is a significant increase in risk for women with benign breast disease to develop breast cancer throughout the following 25 years after diagnosis in comparison to women without benign breast disease (RR=1.56, 95% CI=1.45 - 1.68). However, they found that there is no increased risk among women with non-proliferative lesions, except in cases where there was a strong family history (Hartmann et al., 2005).

In KSA, a few studies have assessed the burden of benign breast disease. One study done through the Saudi National Breast Cancer Screening Program, recruiting 1,215 women between September 2007 and April 2008, found that the 35% of women who scored R4/R5 on the Breast Imaging Reporting and Data System (BI-RADS) system had a benign breast disease (Abulkhair, Al Tahan, Young, Musaad, & Jazieh, 2010). An earlier study (n=953) found that out of the breast biopsies and breast mastectomy obtained, benign breast lesions accounted for 55.24% of all female breast diseases. The distribution of benign lesions among women was fibroadenoma (46.9%), fibrocystic disease (23.25%) and fibroadenosis (14.5%) (Mansoor, 2001). Another hospital-based study from the Western region of KSA reviewed an 8-year data collection of women diagnosed with benign disease and found that 603 out of 1,005 patients given a biopsy were diagnosed with benign lesion (Albasri, 2014). A similar study methodology from the

Eastern region of the country, with a 6-year retrospective review (sample size = 969), found that 60.1% had benign lesions (51.1% were multiple benign lesions), 81.4% had low-risk non-proliferative breast lesions, 14.6% had intermediate-risk lesions without hyperplastic atypia, and 4% had high-risk lesions with atypia (Amin, Al-Mulhim, & Chopra, 2009).

Family History of Breast Cancer

Family history of having breast cancer has been identified as a risk factor for the development of breast cancer in offspring and relatives (Black, 1994; Hartmann et al., 2005). Generally, it has been observed as following an autosomal dominant inheritance with limited penetrance, meaning that some family members may transmit the mutated/abnormal gene without developing the cancer themselves (Black, 1994; McPherson et al., 2000). Although the total number of genes involved in the development of breast cancer among families remains unknown, two have been recognized, BRCA1 and BRCA2, both of which are associated with a very high risk of breast cancer development, especially when four or more close relatives have had breast cancer (McPherson et al., 2000).

A meta-analysis that reviewed 74 studies in 1997 aimed to quantify the risk of breast cancer with family history (Pharoah, Day, Duffy, Easton, & Ponder, 1997). The study observed a significant association with different family history patterns, compared to participants without family history of breast cancer. The relative risk of developing breast cancer amongst women who have had a family member with a history of breast cancer was 1.9 overall (95% CI=1.7 – 2.0) and 2.1 (95% CI=2.0 - 2.2) if the family member was a first-degree relative. The relative risk was 2 (95% CI=1.8 - 2.1) if the family member was the mother, 2.3 (95% CI=2.1 - 2.4) if she was a sister, and 1.8 (95% CI=1.6 - 2.0) if she was a daughter. However, risk was observed to be significantly higher if the participant had both a mother and a sister with the disease, with a relative risk of 3.6 (95% CI=2.5 - 5.0). The relative risk among second-degree relatives was found to be 1.5 (95% CI=1.4 - 1.6). Risk increased in participants below the age of 50 years and if their relatives were diagnosed before the age of 50 years (Pharoah et al., 1997). Other studies had similar findings, which observed a strong and independent association between family history of breast cancer and developing it (Hartmann et al., 2005; Singletary, 2003).

History of Radiation Therapy

Cancer survivors receiving ionizing radiation have been reported to consequently develop breast cancer, based on a few studies. It has been established that this kind of radiation exposure is associated with developing breast cancer amongst women, particularly when the exposure happened during rapid breast formation. For instance, through the use of mailed questionnaires, one study evaluated the overall risk of developing breast cancer after receiving supradiaphragmatic radiation therapy amongst 653 women with Hodgkin lymphoma between 1950 and 1993; median follow-up was 8.7 years. An increased risk of developing breast cancer was observed amongst female cancer survivors of Hodgkin lymphoma who received radiation therapy and who were younger than 30 years. Thirty patients developed breast cancer, with a median interval of 19.9 years since receiving radiation therapy. The standardized ratio observed in this study was 2.9 (95% CI= 2 - 4.2, P<0.001). However, this ratio was 8.5 (95% CI=5.3-13.1) for women younger than 30 years old, compared to 1.2 (95% CI=0.5-2.2) for women aged 30 years or more. (Wahner-Roedler et al., 2003). Another recent study confirmed the significant increase in the risk of developing breast cancer 15 to 30 years after receiving radiation therapy (L. Lee, Pintilie, Hodgson, Goss, & Crump, 2008; Wahner-Roedler et al., 2003).

Overweight and Obesity

Overweight and obesity constitute a public health issue around the world and were found to affect about two billion adults in 2014. Worldwide in 2014, the overall prevalence rate of overweight amongst adults 18 years or older was 39%, 38% in men and 40% in women. However, the overall prevalence rate of obesity during the same year was 13%, 11% in men and 15% in women (World Health Organization, 2012). A cross-sectional study was done in KSA during 2007 on 19,598 individuals in 2,837 households to evaluate the prevalence of obesity through anthropometric measurements. Mainly body mass index, skinfold thickness and mid-arm circumference were measured. The findings were alarming amongst both genders. The obesity prevalence rate amongst women was 23.6% and, at a markedly lower level, its prevalence rate amongst men was 14.2%. However, the opposite situation can be seen with the overweight prevalence rate, with women having a lower rate (28.4%) than men (30.7%) (Al-Othaimeen, Al-Nozha, & Osman, 2007).

The relationship of being overweight or obese with developing breast cancer has been an interesting topic to researchers for decades. Strong evidence has identified body weight, weight changes over time, and various alternative measurements of body size as risk factors for breast cancer (Ballard-Barbash et al., 2009; Glade, 2008; van den Brandt et al., 2000). There is a twofold increase in the risk of developing breast cancer among postmenopausal women when a weight gain of 20-50 pounds occurs, regardless of the baseline body mass index (Ballard-Barbash et al., 2009).

Among women in Saudi Arabia diagnosed with breast cancer, a study observed that 75.8% of them had abnormal weight, leading to an increase in the risk of developing breast cancer by more than twofold (OR = 2.29) when compared to women who had a normal BMI (Alokail et al., 2013; Elkum et al., 2014).

Also, many studies investigated the role of effect modifiers in the relation between body weight and breast cancer, especially in regards to age, menopausal status, and use of hormone therapy (Ballard-Barbash et al., 2009). Obesity has been associated with a reduced risk in breast cancer development among younger or premenopausal women in a few studies (Ballard-Barbash et al., 2009; Glade, 2008; Hunter & Willett, 1993; van den Brandt et al., 2000), but not in postmenopausal women (Chu et al., 1991; De Stavola et al., 1993). And in other studies weight was associated with increased breast cancer risk among postmenopausal women (Ballard-Barbash et al., 2009; Chu et al., 1991; Glade, 2008; Harris, Namboodiri, & Wynder, 1992; Stoll, 1995; van den Brandt et al., 2000; Yong, Brown, Schatzkin, & Schairer, 1996). In postmenopausal women, adipose tissue is an important source of free estrogens and can be a trigger for breast cancer (Clemons & Goss, 2001).

Additionally, evidence from experimental research found that individuals with hyperinsulinemia and genetic predisposition to insulin resistance are at risk of developing breast cancer (high Body Mass Index is associated with the development of hyperinsulinemia) (Del Giudice et al., 1998; Suga et al., 2001). The accumulation pattern of fat in the body varies according to a woman's menopause status, with postmenopausal women usually accumulating fat in the abdomen, which is associated with insulin resistance, higher free estrogen levels, and imbalance in sex steroids levels. These endocrine-metabolic changes are considered a potential catalyst for mammary carcinogenesis that may lead to breast cancer (Stoll, 1995, 1999).

Mammographic Breast Density

The density of breast tissue determined by mammography was found to have a strong association with the risk of breast cancer among women (McCormack & dos Santos Silva, 2006). It was found that women have a higher risk to develop breast cancer by 4-6 times if their breast tissue is composed of over 75% dense tissue on mammography, in comparison to women with very little to no dense breast tissue on the mammography (Byrne et al., 1995). However, it is not completely understood whether high breast density is an independent risk factor or a mediator in the association of other risk factors with developing breast cancer (Rice et al., 2016). In KSA, there is a need to assess the mammographic breast density in the context of the risk for developing breast cancer (Almutlaq et al., 2017).

Dietary Habits

In terms of dietary factors, studies have examined the consumption of animal versus vegetable protein and the potential effect on breast cancer. For example, a study reported that reducing intake of animal protein and having a higher vegetable intake protects against breast cancer. In fact, it was shown that when animal protein is replaced by vegetable protein at an early age (3–5 years of age), lower peak height growth velocity is experienced, which delays the age of menarche. This significantly reduces the risk of developing breast cancer (Berkey, Frazier, Gardner, & Colditz, 1999; Berkey, Gardner, Lindsay Frazier, & Colditz, 2000; Colditz, Bohlke, & Berkey, 2014).

Other studies have examined the association between consuming a Mediterranean diet and breast cancer. For example, in a meta-analysis review by van den Brandt et al. (2017), evidence supported an inverse association between consuming a Mediterranean diet and developing estrogen-receptor negative breast cancer with a strongly protective hazard ratio of 0.60 (95% CI=0.39-0.93). However, a non-significant weak association was seen with the estrogen-receptor positive and total breast cancer risk (van den Brandt & Schulpen, 2017).

Additionally, a meta-analysis found a small statistically significant inverse association between total cholesterol, high-density lipoprotein cholesterol, and the risk of developing breast cancer (Touvier et al., 2015).

In Saudi Arabia, a study was done in 2004 to assess the relation between fat intake and breast cancer in a case-control design. The findings showed a statistically significant increase in breast cancer risk among women with higher fat, protein, and calorie intake, with adjusted odds ratios for the highest versus the lowest quartiles of intake being 2.43 (95% C.I. = 1.36 – 4.34) for saturated fat, 2.25 (95% C.I. = 1.27 – 3.99) for animal protein, 2.12 (95% C.I. = 1.17 – 3.83) for polyunsaturated fat, 1.88 (95% C.I. = 1.03 – 3.44) for cholesterol, 2.16 (95% C.I. = 1.21 – 3.88) for serum triglycerides, and 2.69 (95% C.I. = 1.51 – 4.81) for total energy from dietary intake (Alothaimeen, Ezzat, Mohamed, Muammar, & Al-Madouj, 2004). However, the food at the time of the study mainly included red meat and less vegetables and there has been a change in dietary habits since then, especially with the expansion of fast food restaurants across the country; therefore, a new diet assessment is necessary.

Physical Activity

A review article found that higher physical activity at different ages was inversely associated with breast cancer risk, with findings showing a 16% reduced risk for physical activity at adolescence, 8% for early adulthood, 15% for middle adulthood, and 17% for ages 50 years and older (Lynch, Neilson, & Friedenreich, 2011). Additionally, the effect of adolescent physical activity on breast cancer was investigated in a few studies. For instance, the Nurses' Health Study II noticed a decrease in the risk of developing premenopausal breast cancer among women who had been practicing high levels of physical activity between ages 12 to 22 years by 30% (Risk Ratio = 0.70, 95 % CI=0.53–0.93) versus women with low levels of activity during the same period of age (Maruti, Willett, Feskanich, Rosner, & Colditz, 2008). Additionally, an earlier case control study (1459 cases and 1556 controls) was done in urban Shanghai using interview-questionnaires on women newly diagnosed with breast cancer. The study reported a decrease in premenopausal and postmenopausal risk among women who were physically active in their early life, adolescence and adulthood (Matthews et al., 2001).

Additional findings regarding physical activity and breast cancer were reported by other studies. For example, risk was found to decrease among women who had engaged in exercise during adolescence years (OR = 0.84, 95%CI=0.70–1.00), during adulthood (OR = 0.68, 95%CI=0.53–0.88), and with stronger reduction for those who had exercised during both periods (OR = 0.47, 95%CI=0.36–0.62) (Matthews et al., 2001). Another review indicated that with each additional hour of physical activity per week, there is a decreased risk of developing breast cancer by 6% (95%CI=3%-8%), this trend analysis assumes that an individual maintains the same level of activity over time (Monninkhof et al., 2007). Also, it has been found that recent physical activity could potentially be more protective against breast cancer than activity done in the past (Peters et al., 2009). Furthermore, a recent study showed that the longer the duration and the higher the intensity of physical activity among adults the lower is the risk for breast cancer (Lynch et al., 2011).

In Saudi Arabia, there has been a drastic lifestyle change over the past three decades that has affected the epidemic status of non-communicable diseases across the country, including higher rates of breast cancer (Al-Hazzaa, 2004). In fact, physical inactivity has been increasing among Saudis recently as seen in a study that showed physical inactivity at 96.1% (98.1% among women, 93.3% among men) (Al-Nozha et al., 2007). Another study, a cross-sectional population-based national survey (sample size = 4,758), confirmed the high prevalence of physical inactivity among Saudis with a statistically significant association between gender, geographical location, and employment status. The overall physical inactivity was 66.6% (95% CI=65.3% - 68%) among males 60.1% (95% CI=58.1% - 62.1%), and among females 72.9% (95% CI=71.1% - 74.7%) (Al-Zalabani, Al-Hamdan, & Saeed, 2015). Also, leisure time physical inactivity was observed in the same study to be 87.9%, with 85.6% among males and 90.2% among females. This is very alarming for women's health in KSA, especially with the evidence associating physical inactivity to the development of breast cancer.

Alcohol Consumption

The risk to develop many types of cancer has a well-established association with alcohol consumption and the International Agency for Research on Cancer (IARC) classifies habituating it as a risk factor to develop several cancers including breast cancer (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012). Furthermore, the Centers for Disease Control and Prevention (CDC) in the United States recognized that drinking alcohol increases the risk of developing breast cancer (The Center for Disease Control and Prevention, 2016). Additionally, in a European Prospective Investigation into Cancer and Nutrition, which included a sample of 334,850 women aged 35-70 years at baseline, for each 10 g/day (equivalent to 1 drink per day) increase in alcohol intake (when 0 to 5 g/day of alcohol/day was used as a reference) the hazard ratios increased by 4.2% (95% CI, 2.7–5.8%), while alcohol intake of 5 to

15 g/day was related to a 5.9% increase in the breast cancer risk (95% CI, 1–11%) (Romieu et al., 2015). Thus, the public health message for the women who consume alcohol frequently is to keep it minimal (Ali et al., 2014; Lew et al., 2009).

In KSA, the prevalence of alcoholic beverages consumption was found to be 7.5% in the north of the country (Ginawi, 2013). Alcohol consumption has more social stigma amongst Saudi public and is illegal. Similar to smoking, its prevalence rate is thought to be under-reported (Almutlaq et al., 2017).

However, it is interesting to note that a higher fiber intake (>24.2 g/day) in diet tends to significantly counter the effects of alcohol intake, thereby potentially decreasing the chance of developing breast cancer; the strongest effect was from vegetable fibers, with a hazard ratio of 1.02 (95%CI=0.99-1.05, test for interaction $p = 0.01$). On the other hand, those who drink alcohol and have a low fiber intake (<18.5 g/day) were found to have a significantly increased risk of developing breast cancer, with a hazard ratio of 5.7 (95% CI: 3.2–7.9) per 10 g/alcohol per day. This needs to be further investigated in experimental research to find out the effects of fiber intake in the diet (e.g. via food or supplements) on developing breast cancer (Romieu et al., 2017).

Tobacco Smoking

The risk of developing breast cancer after smoking for years has been investigated by many researchers, and a positive association was observed (Catsburg, Miller, & Rohan, 2015; Johnson et al., 2011). In KSA, the conservative culture and stigma associated with smoking in women challenge the identification of the burden of smoking among Saudi women, and the very low rates are thought to be under-reported (Algorinees et al., 2016; Alshammari et al., 2015).

Thus, more research is needed to identify the burden of smoking and to assess its association with developing breast cancer.

Breast Cancer Screening

Breast cancer screening is effective in reducing mortality form breast cancer, although there is a risk of overdiagnosis and false positive findings (Arrospide et al., 2015).

Over the past few years, breast cancer screening recommendations have been the subject of intense debate among major medical organizations, as controversies around the appropriate age to begin screening and the screening interval were triggered by the release of the US Preventive Services Task Force screening guidelines (US Preventive Services Task Force, 2009). The current guidelines for breast cancer screening released by the American Cancer Society (ACS) in 2015 recommended that women at an average risk to develop breast cancer should have a regular screening mammography starting at the age of 45 years. For women aged 45-54 years, ACS recommends an annual screening. For women aged 55 years and older, ACS recommends a biennial screening or continuing on an annual basis. However, a healthy woman with a life expectancy of 10 years or more should have the choice to start an annual screening between the ages of 40-44 years (Oeffinger, Fontham, Etzioni, & et al., 2015).

In Saudi Arabia, there was no breast cancer screening program prior to 2007. The first program was established in 2007 in Riyadh, the capital city, through a generous charity organization. This program, known as Abdul Lateef Charitable Screening Center, received women for screening year around in collaboration with the Saudi Cancer Registry. Most of the participants came from Riyadh, since the center is located there, but there have been other women who came from all regions of the country. The outcomes that resulted from this program were encouraging enough to expand the breast cancer screening; furthermore, some gaps that relate to women's health awareness have been identified through this program (Abulkhair et al., 2010).

Subsequently, the National Breast Cancer Early Detection Program (NBCEDP) was established by the Saudi Ministry of Health in April 2012. The Saudi NBCEDP has been providing screening to any woman who seeks its services, regardless of socioeconomic status. Since the launch of the NBCEDP and until March 2017, the program had screened about 45,000 women for breast cancer and identified 300 confirmed breast cancer cases (66% of the detected breast cancer cases were at early stage). The guidelines of breast cancer screening in the NBCEDP were to screen women between the ages of 40 to 89 years. Launching the Saudi NBCEDP has provided a big opportunity to understand breast cancer status in the country and inform screening guidelines.

Problem Statement

Breast cancer rates are on the rise in Saudi Arabia. Typically, breast cancer cases have been characterized by a younger age at diagnosis and a later stage at presentation, compared with Western countries. The NBCEDP, although still restricted to the Riyadh region and has not been scaled up nationally, represents a step in the right direction towards improving early detection and prognosis of the disease. However, to achieve prevention and control of breast cancer, additional efforts are needed. One facet of the breast cancer problem in KSA that hampers prevention is the lack of health awareness among women about breast cancer etiology and early detection. Research findings from the program after 8 months of launch were published and showed that there is a lack of health education amongst Saudi women regarding breast cancer etiology and screening due to the conservative nature of the culture and the stigma around breast cancer. The MoH and other health stakeholders in KSA face additional challenges in the effective control and early detection of breast cancer in the country. The current screening guidelines are adopted from Western standards and are not tailored to Saudi women. This is due to the major gaps in knowledge about the epidemiology and etiology of breast cancer in KSA. There is an urgent need for locally relevant research that identifies aspects of breast cancer epidemiology and etiology that are specific to Saudi women.

Purpose Statement and Research Question

To offset some of the above-mentioned research gaps, we conducted a secondary data analysis using population-based data from the only governmental and largest breast cancer screening program in KSA. Our aim was to perform a comprehensive assessment of risk factors for breast cancer among Saudi women.

Significance Statement

This research will provide valuable information that will help understand and better characterize the risk factor profile for breast cancer in Saudi Arabia. Such information will contribute significantly to the current body of evidence on breast cancer etiology and will set the stage for evidence-based prevention efforts that are tailored to Saudi women. The findings and recommendations of this research will be useful for health policy makers, researchers, clinicians and scientists as they work towards a better understanding of breast cancer etiology, reducing breast cancer incidence, and improving early detection and disease prognosis in Saudi Arabia.

Chapter III. Manuscript

Abstract

Background: Breast cancer is the most common malignancy among women worldwide. In Saudi Arabia, the age-adjusted incidence rates for breast cancer have been increasing over time; however, disease etiology remains poorly understood. We performed a secondary data analysis to assess risk factors for breast cancer among Saudi women through analyzing data from the National Breast Cancer Early Detection Program (NBCEDP).

Methods: Data was collected by the NBCEDP between January 2012 and July 2016. During this period, 45,000 women were screened for breast cancer out of which 300 were diagnosed with invasive breast cancer. Our analysis included 8365 screened women (60 confirmed cases and 8305 non-cases) who had data on risk factors collected under a pilot research study conducted by the program. Logistic regression was used to identify associations for breast cancer risk factors with disease risk.

Results: Well-established breast cancer risk factors (such as reproductive factors, personal or family history of breast cancer, overweight or obesity) were not found to vary significantly between cases and non-cases. The only factors to show statistically significant associations with breast cancer risk were level of education (Odds Ratio [OR] for primary, secondary or high school education= 0.13, 95% CI= 0.02 – 0.71; OR for college or postgraduate education= 0.34, 95% CI 0.07 – 1.53, compared to illiteracy) and time spent doing physical activity [hours per week] (OR = 1.03, 95% CI 1.01 – 1.05).

Conclusion: Additional studies using a larger number of cases and employing a longitudinal design are needed to confirm our findings of no association with established risk factors and to further investigate novel risk factors for breast cancer among Saudi women.

Introduction

Breast cancer is the most common cause of cancer incidence and mortality and the fifth leading cause of total mortality in women worldwide (International Agency for Research on Cancer, 2012). The increasing mortality rate is a public health concern given that around 571,000 people died from this disease in 2015, compared to a relatively lower mortality rate in 2012, with around 521,907 deaths (International Agency for Research on Cancer, 2012). In the United States of America (USA), estimates from the American Cancer Society for 2017 indicate that breast cancer is the leading cause of cancer incidence among women, accounting for 252,710 new cases (30% of all cancers), and the second leading cause of mortality, accounting for about 40,610 cancer deaths (14% of all cancer deaths) (American Cancer Society, 2017a).

In both industrial and non-industrial countries, breast cancer is the highest-ranking cancer in terms of incidence among females; however, there are differences between these countries in terms of age at diagnosis, disease stage at presentation, and biological characteristics of breast cancers. For instance, in the United States, about 50% of newly diagnosed breast cancer cases occur among women older than 63 years of age while in non-industrial countries about the same percentage of newly diagnosed cases occurs among women younger than 50 years (Rodríguez-Cuevas et al., 2001). This represents a public health concern, as the diagnosis of disease at an earlier age is correlated with a worse prognosis regardless of menopausal status (Dubsky et al., 2002). Also, the stage of breast cancer at diagnosis differs widely between the two groups of countries, where the patients in non-industrial populations usually seek medical care at an advanced stage of the disease, at the local invasion or metastatic phase, whereas in the industrial countries the disease is detected early by screening and is treated at earlier stages of the disease, including in-situ breast cancer (Li et al., 2005; Murray, 2003).

The Kingdom of Saudi Arabia (KSA) and other countries in the Arabian Peninsula, are non-industrialized countries (World Economic Situation and Prospects, 2014) that have newly adopted a modern lifestyle similar to that of industrialized countries. Although these countries have lower breast cancer incidence rates than industrialized countries (International Agency for Research on Cancer, 2012), they are witnessing an increasing trend in breast cancer occurrence, and projections indicate that incidence rates will continue to rise (Al-Rikabi & Husain, 2012; E. O. Lee et al., 2004). In fact, currently, the age-adjusted incidence rate among Saudi females has been increasing over a 19-year period, from 13.3 per 100,000 in 1994 to 25.5 per 100,000 in 2013, as estimated by the Saudi Cancer Registry (SCR) (Saudi Cancer Registry, 2016). However, there is no national data about mortality rates of this cancer in KSA.

A major problem of breast cancer in KSA is its late presentation and poor prognostic outcomes. The late presentation of breast cancer patients in Saudi Arabia was found to be due to, in part, the Saudi cultural values, where women tend to ignore symptoms while the disease is aggressively attacking. This conservative nature of the Saudi society (such as fear of cancer, shyness, family restrictions, and fear of social implications) and other reasons including poor health awareness and difficulty in accessing health care were considered barriers for Saudi women to seek breast cancer diagnosis and treatment at earlier stages of the disease (Alam, 2006; Amin, Al Mulhim, et al., 2009). The common late presentation among Saudi females with breast cancer has created a difficult situation for them and their families, as well their social lives. This is especially true amongst the youngest patients.

By comparison, in USA, a country with well-established and organized cancer prevention programs, the age-adjusted breast cancer death rate has been decreasing from 30.6 per 100,000 population in 1995 to 20.5 per 100,000 population in 2014 (American Cancer Society, 2017b; Smith & Brawley, 2014). This decrease is due to the efforts that have been done so far to raise public health awareness regarding breast cancer and improving the screening process to expand coverage to the majority of the population (Health Resources and Services Administration, n.d.).

KSA aims to lower breast cancer rates and improve prognosis. The Ministry of Health (MoH) and other health stakeholders in KSA are seeking solutions for breast cancer, including the late presentation patterns found in the country. Ongoing assessment of risk factors, mammography screening, and raising public awareness about disease prevention and early detection are established factors to reduce the incidence and mortality of the disease. To this end, the Saudi MoH established the National Breast Cancer Early Detection Program (NBCEDP) in 2012 in the capital city of Riyadh. The NBCEDP provides screening to any woman who seeks its services. Despite such efforts, there are major gaps in the country related to breast cancer knowledge, as well as the translation of knowledge to programs and policies for breast cancer prevention. Therefore, there is an urgent need in KSA to build a knowledge base on breast cancer etiology and to understand the extent to which well-known risk factors for breast cancer apply to Saudi women. To address this need, we conducted a secondary data analysis using population-based data from the only governmental and the largest breast cancer screening program in KSA. Our aim was to perform a comprehensive assessment of risk factors for breast cancer among women in KSA. This research provides valuable information that will help understand and better characterize the risk factor profile for breast cancer among Saudi women. Such information will contribute significantly to the current body of evidence on breast cancer etiology and will set the stage for evidence-based prevention efforts.

Methods

Study Design

We utilized existing data from the National Breast Cancer Early Detection Program (NBCEDP) and performed a secondary data analysis to assess breast cancer risk factors in women presenting to the program. De-identified data, devoid of personal identifiers, was shared with the study team after approval of the NBCEDP leadership. Data collected between January 2012 and July 2016 was used in our analysis. The study was submitted for review to Emory's Institutional Review Board (IRB) and was determined to be exempt from review.

Data Source and Study Sample

The NBCEDP was established by the Saudi MoH in April 2012 with the goal of providing breast cancer screening and early detection services for eligible women. Women are eligible for participation in the program if they are asymptomatic for breast cancer and are between the ages of 40-89 years or have a family history of breast or ovarian cancer. All women provide consent before participation. The program was initiated in the Riyadh region through two mobile clinics running between health centers and shopping malls. Afterwards, it expanded to five clinics, two of which operated at two prominent shopping malls (Hayat and Panorama malls) on a regular basis and the remaining three being mobile clinics which traveled throughout Riyadh region.

These clinics provide general health screening services such as height, weight and blood pressure measurements. Additionally, they provide clinical breast examinations, mammography screening, and ultrasound breast screening. Moreover, these clinics provide general health education and promoted a healthy lifestyle to help lower the increasing prevalence of non-communicable diseases in the country. A detailed description of the journey for a woman participating in the program is shown below in Figure 1. There were about 45,000 women that the program attended between January 2012 and July 2016. In a pilot study, though the program aimed to collect risk factor data on 10,000 consenting participants presenting for screening by the end of July 2016, it attained a sample size of 8365 participants. Our analysis included all 8365 participants, of whom 60 women were diagnosed to have breast cancer.

Data Collection

In an effort to assess risk factors for breast cancer, the NBCEDP initiated a study in April 2012 to collect risk factor data on a subgroup of women presenting for screening who consented for study participation. Women were administered a brief interviewer-administered questionnaire about breast cancer risk factors by a trained physician. The questionnaire included information on age, reproductive history, history of breastfeeding, postmenopausal hormonal therapy and oral contraceptive use, as well as personal history of breast biopsy or surgery, personal history of breast and ovarian cancer, and family history of cancer.

In addition to the risk factors questionnaire, existing records available at the NBCEDP included mammographic data, pathologic findings and diagnostics. A written consent was obtained from all participants before their participation and after informing them the objective of the program and how the collected data would be used with full confidentiality.

Risk factors data

The program collected data on a broad array of breast cancer risk factors. Reproductive history of the participant was assessed and included: age at menarche (categorized as less than 12 years, 12 years or more), age at first full-term pregnancy [FTP] (categorized as 30 years or more, less than 30 years old, or not applicable), total number of FTPs (categorized as none, 1-4, or 5 or more pregnancies), total number of abortions (categorized as none, 1-2, 3 or more), age at menopause (categorized as less than 45, 45-49, 50-54, 55 or more years). Additionally, the history of breastfeeding was obtained in the form of a question about the duration of lifetime lactation (categorized as less than 6, 6-12, or more than 12 months). In addition, hormone replacement therapy and oral contraceptive usage history was assessed and included a series of questions on overall use (categorized as yes or no) and the cumulative duration of use (categorized as less than 2, 2-5, or more than 5 years). Furthermore, family history of breast and/or ovarian cancer was obtained (categorized as yes or no) and it was followed with further questions about the family member(s) affected (categorized as mother, sister [one or more], daughter [one or more], aunt, and grandmother) and their age at diagnosis. Also, data collection involved personal history of breast or ovarian cancers (yes or no). Other risk factors assessed were history of breast biopsy (categorized as none, one, more than one) and history of breast abnormalities (defined as at least one breast biopsy with atypical hyperplasia[1] and categorized as [No, Yes, I don't know]). Moreover, history of a previous exposure to mantle radiation for

[1] The National Cancer Institute define it as "A benign (noncancerous) condition in which cells look abnormal under a microscope and are increased in number" (N. The National Cancer Institute, n.d.)

treating Hodgkin's Lymphoma between 10-30 years of age was assessed (categorized as No, Yes, I don't know).

Anthropometric assessments were obtained via direct measurement. Height (in centimeters) was measured on a fixed stadiometer and weight (in kilograms) was measured on a balanced beam scale using lightweight clothes. The Quetelet's Index was used to calculate Body Mass Index (BMI), by dividing weight in kilograms by the square of height in meters. Following BMI calculation, the BMI was categorized into four classes using the WHO criteria (underweight < 18.50 Kg, normal range 18.50 – 24.99 Kg, overweight ≥ 25Kg, and obese ≥ 30.00 Kg) (WHO, 2017a).

Mammography findings

Women of age between 40 and 89 years old received a mammographic imaging. The results of the imaging were interpreted based on the classification of the American College of Radiology (ACR)'s Breast Imaging Reporting Data System (BI-RADS), as follows: breast findings (categorized as mass, calcification, density, focal asymmetric density, multiple bilateral masses, multiple bilateral calcifications, multiple bilateral calcifications and masses, architectural distortion, and other findings), characteristics of the breast (categorized as density, size, shape, margin) and the characteristics of calcifications (by type and distribution), and locations of the breast finding (categorized as upper, upper outer, outer, lower outer, lower, lower inner, inner, upper inner, and central or retro-areolar), the depth of the finding (categorized as anterior, middle, or posterior) (American College of Radiology, 1996). The BI-RADS assessment was categorized on a six-point numeric scale as follows: 0 (assessment incomplete; therefore, additional evaluation is recommended), 1 (negative / normal; therefore, continuation of routine screening is recommended), 2 (benign finding; therefore, continuation of routine screening is recommended), 3 (probably benign finding; where short-term follow-up mammogram at 6 months, then every 6 to 12 months for 1 to 2 years is recommended), 4 (suspicious abnormality; therefore, perform biopsy, preferably needle biopsy is recommended), 5 (highly suspicious of malignancy; appropriate action should be taken. Biopsy and treatment, as necessary), 6 (known biopsy-proven malignancy; completion of treatment is recommended) (N. The National Cancer Institute, n.d.). Based on this classification, a radiologist recommended to each participant a specific course of action (normal interval screening, request additional mammographic views, ultrasound, fine-needle aspirate, or breast biopsy). The categorization process by the radiologist is known to be a valid and reliable assessment and is strongly recommended for the detection of breast cancer (Liberman & Menell, 2002) (Eberl, Fox, Edge, Carter, & Mahoney, 2006).

Pathologic findings

All suspicious mammography results were sent to the pathohistology laboratories at King Fahad Medical City in Riyadh to evaluate and confirm whether the case is a benign tumor or a cancer of the breast tissues.

Clinical data

At the time of the screening visit, women were offered a clinical breast examination by a primary healthcare physician or a gynecologist. The examination process entailed a visual inspection and palpation of the entire breast followed by a rotational movement with the finger pads at all breast quarters including the axillae and supraclavicular triangles. The visual inspection of the breast was done while it is in the erect and supine positions, upright only for women with small fatty breasts. The palpation of the breast was done while it is in the supine position, upright for women with small fatty breasts with arms overhead and the patient turned to the contra- and ipsilateral oblique positions, as necessary. The technique that was used to examine the breast was the spoke search pattern, which is examining wedges of the breast tissue starting at the periphery of the breast toward the nipple in a radial pattern (Freund, 2000). The data/findings were organized to include information about breast changes (categorized as discrete mass, lump, pain, size, shape, areas of asymmetric thickening), nipple changes (categorized as bloody or serous discharge, inversion, areolar skin retraction, or rash), skin of breast area changes (categorized as dimpled, scaly, or changed color), and lymph nodes enlargement.

Modification to data collection

The questionnaire utilized in the program was modified over time. The new version (2^{nd}) was an improvement of the first version and was launched in November 2013. The revised version included new questions on level of education, dietary habits, and physical activity and sedentary behavior. As such, women who presented to the program before November 2013 did not have data on education, diet and physical activity. The level of education, in the new questionnaire, was categorized as illiterate, primary school completed, secondary school completed, high school completed, college/university completed, and post-graduate degree obtained. The assessment of physical activity was based on a one-year recall of the type of physical activity that the participant engaged in – whether it is leisure, occupational, or housework. This scale was adapted from a previous study that found a significance protection against breast cancer for women who are physically active (Thune, Brenn, Lund, & Gaard, 1997). The overall physical activity level was categorized into: inactive (spending leisure time reading, watching television, or any other sedentary activity), irregularly active (spending some time walking, bicycling, or any other activity during the week), or regularly active (following a regular training or practicing any type of high impact physical activity for at least two hours and a half per week). Similarly, the assessment of dietary habits was obtained as a one-year recall of the participant's diet. This was assessed through questions obtained from validated dietary assessment tools used in a previous study (Martinez-Gonzalez et al., 2012) and the WHO (WHO, 2017b). Dietary habits included an assessment of meat intake (none, 1-2, more than 2 servings/week), an assessment of fresh vegetables and fruits intake (none, 1, 2-4, 5 or more servings/week), and an assessment of fresh vegetables and fruits intake (none, 1, 2-4, 5 or more servings/day). Also, the new questionnaire gathered data on the type of oil and/or fat used in diet (vegetable oil, animal fat, butter, margarine, or olive oil). In addition to introducing new variables as described above, the new version of the questionnaire included modifications to some of the existing variables.

Data Management

Data collected by the NBCEDP included the mammography findings, the risk factors questionnaire, and the biopsy results. Data was stored on secured portable storage devices and special desktops that were accessible only to the program team members. Data entry was done by six staff members, five doctors who interviewed participants and a data management specialist hired by the program. SPSS (version 21) was used for data entry. All data entry personnel had received appropriate training on data entry using this software. Two databases were created by the program: the first included participants who completed the old version of the questionnaire and the second included those who completed the new version. To ensure confidentiality, each participant was assigned a unique identifier at the time of data collection. All personal identifiers were removed before the data was shared by the NBCEDP with the study team. Several data management and cleaning steps were performed by the study team before merging the two databases. A new set of variables was created, as necessary, to harmonize both versions of the questionnaires. Character variables were transformed to numerical variables. Additional data cleaning steps included duplicate data entry checks, outlier identification, and checks for miscoding of variables and missing data patterns. After these steps, the two databases were merged to create a master dataset that includes a set of variables that are common to the old and new questionnaire, a set of variables that are unique for the new questionnaire, and an identifier that flags whether a woman completed the old or the new questionnaire. A unified codebook was created for the master dataset. Our analyses used the merged master dataset.

Data Analysis

Descriptive data analysis (mean, median, and standard deviation for continuous variables and percentages for categorical variables) was conducted to describe the baseline characteristics of participants. Comparison of key characteristics and risk factors between cases and non-cases was performed using t-test for continuous normally distributed variables and Chi-square or Fisher's tests for categorical variables. Next, logistic regression was used to assess associations between risk factors and breast cancer occurrence. Variables were selected for entry into the logistic regression model if they showed associations with breast cancer in bivariate analysis at the 0.15 level of statistical significance. Some variables (age, age at menarche, menopause status) were forced in the model although they were not statistically significant in the bivariate analysis, due to their well-known associations with breast cancer risk. Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained. The final model was adjusted for: age, age at menarche, menopause status, education level, duration of contraceptive use, duration since stopping contraceptive use, and time usually spent doing physical activity. Except for variable selection into the regression model, the level of statistical significance was set at alpha = 0.05. SAS software (version 9.4, SAS Institute Inc., Cary, NC) was used for statistical analysis.

Sample size calculation

We used the formula of Peduzzi et al. (1996) to estimate the minimum number of participants needed for multiple logistic regression. The formula is: N = 10 k / p; where: N= sample size, K= number of independent variables in the model, p= proportion of breast cancer cases in the population. Assuming p= 0.007 (observed proportion of breast cancer in the screened population) and k= 5, we estimated that a sample size of 7,143 would be needed. In the data analysis phase, due to missing data, the effective size was lower than the estimated sample size (Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996).

Results

Association of Risk Factors with Breast Cancer Occurrence

<u>*Bivariate Analysis*</u>

A comparison of characteristics and risk factors profile between cases and non-cases is presented in Table 1. The mean age for breast cancer cases was 50.8 year (SD= 8.0) and was not statistically significantly different from the mean age of non-cases (mean= 50.4 year, SD= 7.9, p-value= 0.74).

In terms of level of education, 29.0% of women who had breast cancer were illiterate, 32.3% completed primary, secondary or high school education, and 38.7% completed college or postgraduate education. We found that the level of education did not vary statistically significantly between cases and non-cases (p-value= 0.15).

Age at menarche was approximately 13.0 years among all women and was rather constant across cases (mean=13.0, SD=1.9) and non-cases (mean=13.2, SD=1.7; p-value=0.34). Evaluating age at menarche categorically, 50% of cases were observed to have an early age at menarche compared to 42% of non-cases; however, this difference was not statistically significant (p-value= 0.45).

Age at menopause was around 50.3 years among all women with 58.3% of cases had not gone through menopause at the time of diagnosis. The age at menopause was rather constant across cases (mean=50.7 year, SD=5.0) and non-cases (mean=50.3, SD=5.5; p-value=0.74). Furthermore, 92.0% of cases had an age at menopause of 45 years or more compared to 86.6% of non-cases; however, this difference was not statistically significant (p-value=0.57).

Age at first marriage was around 18.5 years among all women. The age at first marriage was rather constant across cases (mean=18.8 year, SD=4.6) and non-cases (mean=18.5, SD=4.8; p-value=0.79). Furthermore, 100% of cases had an age at first marriage of less than 30 years compared to 98.1% of non-cases; however, this difference was not statistically significant (p-value=0.63).

In terms of pregnancy status, 98.3% of cases and 95.0% of non-cases have been pregnant (p-value= 0.37). Age at first live birth was slightly higher in cases (mean= 21.2 years) compared to non-cases (mean= 20.5 years); however, the difference was not statistically significant (p-value= 0.22). Approximately 13.6% of breast cancer cases had their first live birth at the age of 30 years or after, compared to 10.7% in non-cases. In terms of the number of pregnancies and number of children, differences observed between cases and non-cases were not statistically significant (p-values= 0.61 and 0.34, respectively).

In terms of breastfeeding, 87.6% of all women did breastfeed prior to participation. There was 86.7% of cases compared to 87.6% of non-cases who had a history of breastfeeding. However, the difference in history of breastfeeding was not statistically significant (p-value= 0.83). The duration of cumulative breastfeeding was lower in cases (mean= 75.9 months) compared to non-cases (mean= 80.1 months); however, this difference was not statistically significant (p-value= 0.64).

The history of use of contraceptive pills use was found to be constant in women who developed breast cancer (85.0%) compared women who did not develop it (85.2%, p-value= 0.96). Additionally, the mean duration of lifetime use of contraceptive pills was longer among women who developed breast cancer (mean= 92.5 months) compared to women who did not develop breast cancer (mean= 77.1 months), although this difference did not reach statistical significance (p-value= 0.14). On the other hand, we found that the average number of years since the women stopped utilizing contraceptive pills was statistically significantly higher in women who developed breast cancer (mean= 17.3 years) compared to those who remained cancer free (mean= 13.1 years; p-value= 0.03). Furthermore, there were 62 women in our study who reported using postmenopausal hormonal therapy; however, none of them developed breast cancer.

Additionally, a few women had a personal history of breast cancer (N= 17) and ovarian cancer (N= 5) before presenting to the NBCEDP.

Family history of breast or ovarian cancer was not statistically significantly associated with breast cancer. In terms of family history of breast cancer, 13.3% of cases and 9.7% of non-cases reported a family history of the disease (p-value= 0.35). In addition, 0.0% of cases and 0.2% of non-cases reported a family history of ovarian cancer (p-value= > 0.99).

No difference in BMI was reported between cases (mean= 34.1 kg/m^2) and non-cases (mean= 33.5 kg/m^2; p-value= 0.49). Among women who developed breast cancer, around half performed regular physical activity during the week, compared to 54.1% among those who were cancer free (p-value= 0.81). With regards to the amount of physical activity, the mean time spent doing physical activity in hours per week was higher among women who developed breast cancer (mean= 38 hours/week), in comparison to women who did not develop breast cancer (mean= 29 hours/week; p-value= 0.07). On the other hand, the mean time spent sitting or reclining in hours per day was about the same among all women regardless of breast cancer status (p-value= 0.68).

In terms of dietary habits, most of the women were utilizing a non-animal source of oil or no oil/fat (96.8% of cases and 99.2% of non-cases, p-value= 0.22). Additionally, among women who developed breast cancer, around half were having at least one serving of vegetables and fruits per week and most of them were having at least one serving of red meat per week; differences between cases and non-cases for both variables were not statistically significant. Of note, dietary habits and physical activity were not in the old version of the questionnaire and thus the sample size for these variables is smaller than other variables (n=3314).

All participants in the study did not have a history of exposure to mantle radiotherapy (Table 1).

Multiple Logistic Regression Analysis

The final model was adjusted for age, age at menarche, menopause status, education level, duration of contraceptive use, duration since stopping contraceptive use, and time usually spent doing physical activity (N= 7125).

In the adjusted logistic regression model, the level of education and the time usually spent doing physical activity (hour per week) were the only variables to show a statistically significant association with breast cancer occurrence. In comparison to women who were illiterate, the odds of breast cancer were 87% lower in women who had a primary, secondary or high school level of education (OR= 0.13, 95% CI= 0.02 – 0.71) and 66% lower in those with a college or postgraduate level of education (OR= 0.34, 95% CI= 0.07 – 1.53) ; however, the association for the latter education category did not achieve statistical significance. In terms of time usually spent doing physical activity, the odds of breast cancer were 3% higher with each hour per week a woman spent doing physical activity (OR= 1.03, 95% CI= 1.01 – 1.05). None of the other variables showed statistically significantly associations with breast cancer (Table 2).

Clinical and mammographic findings in breast cancer cases and non-cases

The majority of women were presenting to a first mammogram (86.7% of cases and 86.6% of non-cases). A positive finding on the breast clinical examination was observed in 30.0% of cases and 2.4% of non-cases (p-value < 0.0001). A suspicious finding on the mammography was observed in 79.7% of cases and 6.9% of non-cases (p-value < 0.0001) (Table 3).

Discussion

We performed an assessment of breast cancer risk factors among women presenting to the National Breast Cancer Early Detection Program in Saudi Arabia. Well-known breast cancer risk factors, such as reproductive factors, were not found to vary significantly between cases and non-cases. Level of education and time spent doing physical activity were the only factors to show a statistically significant association with breast cancer risk.

While there were no studies from Saudi Arabia investigating the relation between the level of education among Saudi women and developing breast cancer, we observed in our study promising results. A higher level of education was associated with a lower odds of developing breast cancer, a finding that encourages more investment in women's education and public health awareness.

Our results regarding physical activity are contrary to what is reported in the literature. While our study showed a 3% higher odds of breast cancer with each hour per week a woman spent doing physical activity, the literature estimates a lower risk of developing breast cancer with a longer duration and a higher intensity of physical activity (Lynch et al., 2011). This difference in findings could be attributed to variations in the methods of measuring physical activity across studies and to the quality of measurement. An accurate assessment of physical activity among Saudi women requires valid and reliable tools that are contextualized to the conservative nature of the society.

Age at diagnosis of breast cancer among women in this population-based study was consistent with the age at diagnosis reported by the Saudi Cancer Registry (approximately 50 years) (Saudi Cancer Registry, 2016) and was also close to the estimated average age at diagnosis of breast cancer reported in other Arabian Peninsula and Arab countries (48 years) (Najjar & Easson, 2010). However, this age of diagnosis among Saudi women is remarkably lower than that reported in developed countries (61 years), a difference that remains not fully understood (The National Cancer Institute, 2015). Therefore, there is a need for further investigation of the etiology behind early-onset breast cancer among Saudi women.

Assessing breast cancer risk factors, we observed that age was not associated with disease risk. Similarly, reproductive risk factors did not vary significantly between cases and non-cases. This finding is interesting and can be partially explained by the low variability among Saudi women, whether cases or non-cases, in their reproductive profile. For example, 98.3% of cases and 95% of non-cases were ever been pregnant. Similarly, the large majority of women had a first live birth before the age of 30 years (86% of cases and 89% of non-cases). A larger sample size may be required to detect statistical significance against this homogeneity in reproductive risk.

A study that examined several studies to look into the correlation between breastfeeding and risk of developing breast cancer found that the longer duration of breastfeeding is protective against developing breast cancer in many places around the world (Chowdhury et al., 2015). Interestingly, our data points to an opposite trend, albeit not statistically significant, where cases had a longer cumulative period of breastfeeding compared to non-cases.

It is known that cases of breast cancer occur more commonly among postmenopausal women, particularly in developed/industrialized countries (Ghiasvand, Adami, Harirchi, Akrami, & Zendehdel, 2014). In our study, we saw an opposite observation where the proportion of women who were postmenopausal at the time of diagnosis was 41.7%. However, menopause status was not statistically significantly associated with breast cancer risk.

Oral contraceptive use had been inconsistently correlated with developing breast cancer depending on whether history of oral contraceptive use, duration of use, age at initiation, or time since stopping was evaluated. The starting age of using oral contraceptive was correlated with developing breast cancer among women with BRCA 1 gene mutation (Kotsopoulos et al., 2014). Other studies, evaluating different formulations of oral contraceptives, found inconclusive or non-significant associations between oral contraceptive use and developing breast cancer (Hunter et al., 2010; Marchbanks et al., 2012; Zhu et al., 2012). Similarly, there is no clear evidence in the literature about the relationship between years since stopping oral contraceptive use and developing breast cancer. Our study revealed a trend where a longer time since stopping oral contraceptives was associated with a higher breast cancer risk; however, this association became not statistically significant in the fully adjusted model. Therefore, our study confirms what most of the literature found in that history of oral contraceptive use, duration of use, or time since stopping were not risk factors for breast cancer.

Contrary to other studies (McPherson et al., 2000), family history of breast or ovarian cancer was not associated with developing breast cancer among women in our study. Specific genes, such as BRCA1 and BRCA2, are known to increase breast cancer risk via an autosomal dominant familial transmission (McPherson et al., 2000). The only published population-based breast cancer study in Saudi Arabia was consistent with ours and showed no association between family history of breast cancer and developing the disease (Abulkhair et al., 2010).

Our study has several limitations. The small number of cases had implications on estimates – it resulted in wide conference intervals and may have explained the lack of statistically significant associations for known risk factors of breast cancer with disease risk. Studies with a larger number of cases are needed to confirm our findings. In addition, we could not assess risk factors like cigarette smoking and alcohol consumption because they were not measured. Thus, we encourage future clinical and public health researchers to actively collect data on these variables in a way where women in Saudi can feel comfortable reporting on their behavior without feeling stigmatized. A main limitation of our study is the lack of data on breast density, which is a major risk factor for developing breast cancer (McCormack & dos Santos Silva, 2006). Breast density may be a particularly important risk factor in our population where none of the other classic risk factors like reproductive variables was found to be associated with breast cancer risk. Furthermore, no study has characterized breast density in Saudi women. We recommend that the Saudi NBCEDP introduces this measurement in its screened population. Another limitation is the lack of data on hormone receptor status of tumors. This precluded an assessment of breast cancer risk factors for separate tumor subtypes although we know that there is heterogeneity in breast cancer etiology across the different disease subtypes. In addition, characteristics of women who presented to the NBCEDP may not be representative of women in the general population of Saudi; therefore, our results may not be generalizable to the entire population. Also, the modification in data collection precluded an assessment of important risk factors, such as dietary variables and physical activity, among all women. Lastly, the study is cross-sectional in nature; therefore, it does not yield a high level of evidence on causality and does not allow for follow-up to evaluate breast cancer prognosis.

To our knowledge, this study is the largest in Saudi Arabia and most comprehensive in terms of its assessment of a broad range of breast cancer risk factors. Additionally, it is the only population-based study that investigated well-known risk factors for breast cancer among women in Saudi.

In summary, our study revealed interesting observations compared to the literature. Amongst the known breast cancer risk factors, only level of education and time spent doing physical activity were associated with breast cancer risk among women in Saudi Arabia. However, age, reproductive history, breastfeeding, menopause status, postmenopausal hormonal therapy, oral contraceptive pills, personal or family history of breast cancer, history of mantle radiation exposure, obesity, and dietary habits were not found to vary significantly between breast cancer cases and non-cases. Additional studies using a larger number of cases and employing a longitudinal design are needed to confirm our findings and further investigate breast cancer etiology and prognosis among Saudi women.

Figures

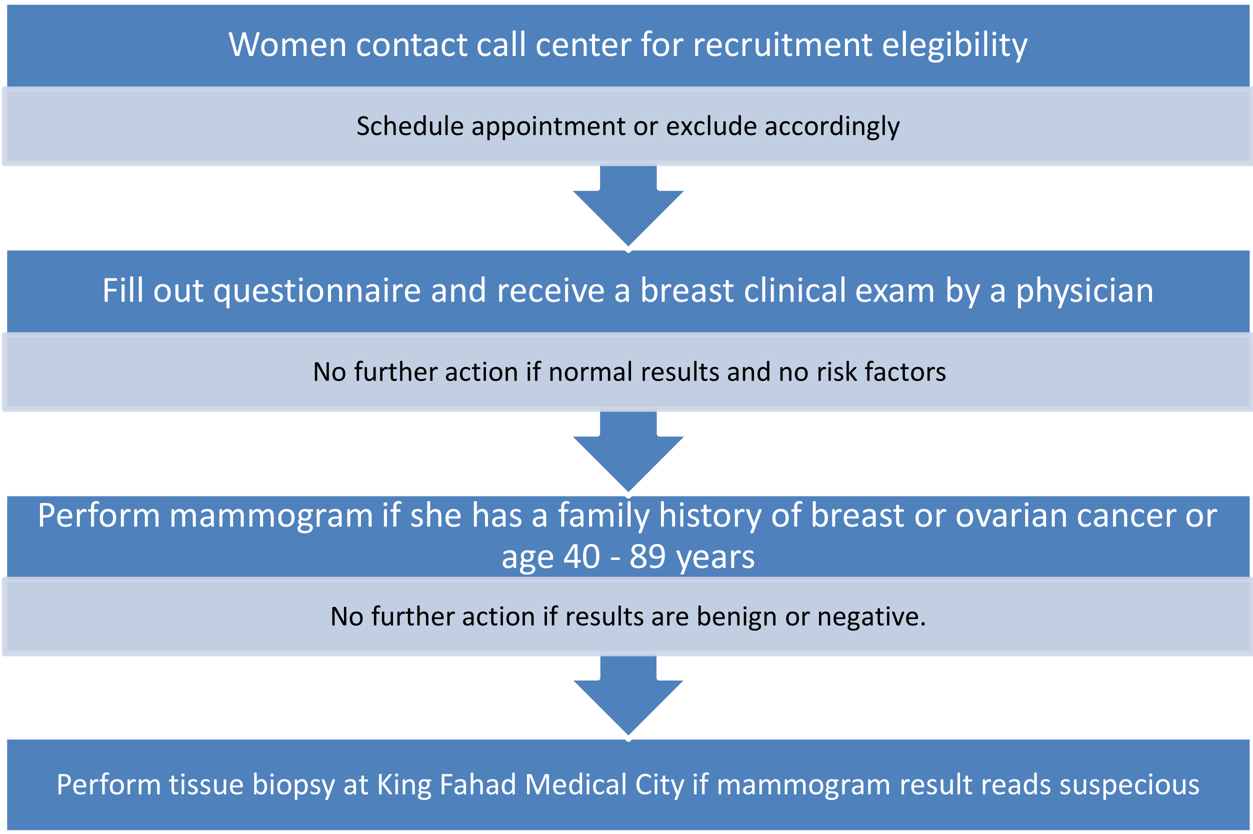

Figure 1. A framework showing the journey for a woman participating in the National Breast Cancer Early Detection Program

Tables

Table 1. Comparison of breast cancer risk factors [(mean ± SD or N (%)] between breast cancer cases and non-cases in women attending the Saudi National Breast Cancer Early Detection Program

Risk Factor	**Cases N=60**	**Non-cases N=8305**	**P-value**
Demographic characteristics			
Age (years)	50.8 ± 8.0	50.4 ± 7.9	0.74
Level of education completed*			
Illiterate	9 (29.0%)	966 (29.5%)	0.15
Primary, secondary or high school	10 (32.3%)	1512 (46.1%)	
College or post-graduate	12 (38.7%)	801 (24.1%)	
Reproductive risk factors			
Age at menarche (years)	13.0 ± 1.9	13.2 ± 1.7	0.34
Early age (< 12)	30 (50.0%)	3483 (41.9%)	0.45
Normal age (12-15)	20 (33.3%)	3260 (39.3%)	
Late age (>15)	10 (16.7%)	1562 (18.8%)	
Menopause status			
Pre-menopausal	35 (58.3%)	4876 (58.7%)	0.95
Menopausal	25 (41.7%)	3427 (41.3%)	
Age at menopause (years)$	50.7 ± 5.0	50.3 ± 5.5	0.74
< 45	2 (8.0%)	460 (13.4%)	0.57
≥ 45	23 (92.0%)	2967 (86.6%)	
Age at first marriage (years)$	18.8 ± 4.6	18.5 ± 4.8	0.79
< 30	59 (100%)	8009 (98.1%)	0.63‡
≥ 30	0 (0.0%)	155 (1.9%)	
Ever pregnant			
No	1 (1.7%)	411 (5.0%)	0.37
Yes	59 (98.3%)	7882 (95.0%)	
Age at first live-birth (years)$	21.2 ± 5.4	20.5 ± 4.7	0.22
< 30	51 (86.4%)	7042 (89.3%)	0.47
≥ 30	8 (13.6%)	840 (10.7%)	

Number of pregnancies	7.5 ± 3.4	7.3 ± 3.7	0.61
Number of full-term pregnancies	5.9 ± 2.6	6.4 ± 2.8	0.34
History of breast feeding No Yes	 8 (13.3%) 52 (86.7%)	 1006 (12.4%) 7113 (87.6%)	 0.83
Lifetime duration of breast feeding (months)[$] 0 - 6 > 6	75.9 ± 67.6 58 (96.7%) 2 (3.3%)	80.1 ± 64.7 7734 (93.1%) 571 (6.9%)	0.64 0.44
History of contraceptive pills use No Yes	 9 (15.0%) 51 (85.0%)	 1226 (14.8%) 7077 (85.2%)	 0.96
Lifetime duration of oral contraception use (months)[$] 0 - 10 > 10	92.6 ± 80.6 21 (35.0%) 39 (65.0%)	77.1 ± 68.5 3386 (40.8%) 4919 (59.2%)	0.14 0.36
Years since stopping the use of contraceptive pills* Never used it Actively using Up to < 10 10 up to 20 +20	17.3 ± 16.4 9 (28.1%) 3 (9.4%) 6 (18.8%) 7 (21.9%) 7 (21.9%)	13.1 ± 8.3 1226 (37.6%) 224 (6.9%) 627 (19.2%) 735 (22.5%) 453 (13.9%)	0.03 0.64
History of postmenopausal hormone therapy use No Yes	 60 (100%) 0 (0.0%)	 8242 (99.3%) 62 (0.7%)	 > 0.99
History of exposure to mantle radiotherapy No Yes	 60 (100%) 0 (0.0%)	 8304 (100%) 0 (0.0%)	 > 0.99
Family history of breast and ovarian cancer in a first/second-degree relative			
Family history of breast cancer Negative Positive	 52 (86.7%) 8 (13.3%)	 7495 (90.3%) 809 (9.7%)	 0.35
Family history of ovarian cancer Negative Positive	 60 (100%) 0 (0.0%)	 8220 (99.0%) 85 (1.0%)	 > 0.99

Personal history of breast and ovarian cancer			
Breast cancer Negative Positive	 60 (100%) 0 (0.0%)	 8288 (99.8%) 17 (0.2%)	 > 0.99
Ovarian cancer Negative Positive	 60 (100%) 0 (0.0%)	 8300 (99.9%) 5 (0.1%)	 > 0.99
Anthropometry and physical activity			
Body Mass Index (kg/m^2) Underweight Normal weight Overweight Obese Morbidly obese	34.1 ± 6.1 10 (16.7%) 3 (5.0%) 11 (18.3%) 14 (23.3%) 22 (36.7%)	33.5 ± 6.3 1414 (17.0%) 431 (5.2%) 1595 (19.2%) 2352 (28.3%) 2513 (30.3%)	0.49 0.85
Regular weekly physical activity * No Yes	 14 (43.8%) 18 (56.3%)	 1504 (45.9%) 1773 (54.1%)	 0.81
Time usually spent doing physical activity (hours/week)*$	38.7 ± 21.4	29.9 ± 20.1	0.07
Time usually spent sitting or reclining (hours per day) *	5.3 ± 2.6	5.5 ± 2.9	0.68
Dietary habits			
Number of vegetables and fruits servings per week* None or less than one serving At least one serving	 17 (53.1%) 15 (46.9%)	 1726 (52.6%) 1556 (47.4%)	 0.95
Number of red meat servings per week* None At least one serving	 4 (12.5%) 28 (87.5%)	 264 (8.1%) 3017 (91.9%)	 0.32
Type of oil / fat used for meal* Non-animal source of oil or no oil/fat Animal fat, non-animal oil, butter, or margarine	 30 (96.8%) 1 (3.2%)	 2969 (99.2%) 23 (0.8%)	 0.22

* Collected on the 2nd version of the questionnaire, and therefore is missing for N= 5055 women.
$ Data was not available on all women; the effective sample size was reduced (N<8365).
‡ Fisher's Exact Test was used.

Table 2. Association of risk factors with breast cancer risk in women attending the Saudi National Breast Cancer Early Detection Program

Risk factor	Odds Ratio*‡	95% confidence interval
Level of education		
Illiterate (Reference Group)	1	
Primary, secondary or high school education	0.13	0.02 – 0.71
College or postgraduate education	0.34	0.07 – 1.53
Time usually spent doing physical activity (hours/week)	1.03	1.01 – 1.05

*Adjusted for age, age at menarche, menopause status, education level, duration of contraceptive use, duration since stopping contraceptive use, and time usually spent doing physical activity.
‡ N=1062

Table 3. Comparison of clinical and mammographic findings [mean ± SD or N (%)] between breast cancer cases and non-cases in women attending the Saudi National Breast Cancer Early Detection Program

Breast cancer screening variables	Cases N=60	Non-cases N=8305	P-value
New mammogram exam or rescreening			
New	52 (86.7%)	7193 (86.6%)	0.99
Rescreening	8 (13.3%)	1112 (13.4%)	
Number of mammograms done before*			
0	24 (75.0%)	2170 (66.2%)	0.53
1	7 (21.9%)	896 (27.3%)	
+2	1 (3.1%)	212 (6.5%)	
Clinical breast exam result‡			
Negative findings	42 (70.0%)	8102 (97.6%)	< 0.0001
Positive findings	18 (30.0%)	203 (2.4%)	
Mammogram result‡			
Non-suspicious findings	12 (20.3%)	7709 (93.1%)	< 0.0001
Suspicious findings	47 (79.7%)	572 (6.9%)	

* Collected on the 2nd version of the questionnaire, and therefore is missing for N= 5055 women.
‡ Fisher's Exact Test was used.

Chapter IV. Implications and Recommendations

In Saudi Arabia, there is a big gap in our understanding of the epidemiology and etiology of breast cancer. Our study explored and analyzed data collected by the Saudi NBCEDP in the context of assessing risk factors of breast cancer among Saudi women. The analysis revealed that compared with illiterate women, those with a higher educational level had a lower risk of breast cancer. Also, women with higher levels of regular physical activity had a higher risk of breast cancer compared to women who were less physically active. Additionally, our study found that well-known breast cancer risk factors, such as reproductive risk factors, were not associated with disease risk in Saudi women. Our findings add to the scientific literature in Saudi Arabia and uncover questions related to breast cancer etiology that require further investigation. They also yield specific recommendations for the MoH's NBCEDP. These findings and recommendations will be useful for health policy makers, researchers, clinicians and scientists as they work towards a better understanding of breast cancer etiology, reducing breast cancer incidence, and improving early detection and disease prognosis.

Our recommendations to the NBCEDP include:

1) Expanding screening and data collection to all regions in the country. In addition to extending the benefit of screening and early detection to all women, this will also improve the representativeness of data collected by the program and will allow for a larger sample size and higher statistical power to detect associations between risk factors and breast cancer risk.

2) Adding other important risk factors to the portfolio of data collected by the program, particularly breast density and tumor subtype.

3) Improving the quality of data collected, particularly for the physical activity and diet questions to reduce information bias.

4) Considering a longitudinal study design where women are followed up after diagnosis to enable an evaluation of breast cancer outcomes, including survival, as well as prognostic factors.

Our recommendations to the research community include:

1) Understanding the etiology of early-onset of breast cancer among women in Saudi Arabia.
2) Confirming the findings of no association between well-established risk factors for breast cancer and disease risk among women in Saudi Arabia using larger sample size and longitudinal study designs.
3) Evaluating novel risk factors for developing breast cancer such as breast density and the ongoing discovery of genetic risk factors.
4) Conducting studies to better understand breast cancer survival and prognostic factors.

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