Updated Key Determinants of Breast Cancer Risk in Bahrain: A Comprehensive Analysis

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ABSTRACT

Breast cancer is the most common cancer, and the second leading cause of death in women globally. In Bahrain, female age-standardized cancer incidence is the third highest (137.4 per 100,000 people) in the Arabian Gulf. The 3 common cancers in Bahraini females are breast (58.5 per 100,000 people), followed by colorectal (12.4 per 100,000 people), and uterine (8.2 per 100,000 people) cancers. Most cancers are related to lifestyle, genetic predispositions,mand environmental factors. Breast cancer awareness campaigns are crucial for early detection and better outcomes. Lifestyle modifications also play an important role in cancer prevention. Advanced-stage diagnosis is still seen, so more community awareness efforts are needed. There are still few studies published on the risk factors of breast cancer in Bahrain. To assess the primary risk factors of breast cancer in Bahrain. All patients were operated on by 2 senior consultant surgeons in Bahrain. Design: Prospectively collected patients' data and analyzed using SPSS. Two hundred twenty-six consecutive breast cancer patients in the period from August 1999 to August 2020. Risk factors studied included: age at diagnosis, early menarche age (11 years and below), and late menopause age (50 years and above). Other factors included parity or nulliparity, late age at first full- term pregnancy (more than 30 yrs.), history of lactation, prolonged history of uninterrupted use of Oral Contraceptive Pills (OCP) (more than 5 years), prolonged history of uninterrupted use of Hormonal Replacement Therapy (HRT) (more than 2 years), past personal history of breast, ovarian or other cancers, family history of breast, ovarian or other cancers, presence of Diabetes, and weight of patients at presentation. All patients were females. The age of patients at diagnosis was categorized into 2 categories. The first category result was as follows: less than 35 years old were 21 patients (9.3%), 35-45 years were 61 patients (27%), 46-55 years were 84 patients (37.2%), and more than 55 years old were 60 patients (26.5%). The second category was as follows: 20 to 29 years were 4 patients (1.8%), 30 to 39 years were 38 patients (16.8%), 40 to 49 years were 77 patients (34.1%), and 50 years and above were 107 patients (47.3%). Early menarche (11 years and below) was observed in 40 patients (20.2%), and those who attained menopause were 97 patients (43.1%). Forty-seven patients were Nulliparous (20.8%). One hundred fifty-four patients (81.1%) had their first pregnancy at less than 30 years old. Lactation history was negative in 62 patients (27.6%). Fifty-four patients (24.5%) used OCP for long periods. Six patients (2.7%) took HRT. Five patients (2.2%) had a positive personal history of malignancy (Breast, ovaries & others). Seventy-eight patients (34.8%) had a positive family history of cancer. Thirty patients (18.3%) had Diabetes, and the weight of the patients was at or above the standard adult weight (70 Kg) in one hundred twenty-two (58.4%). The studied group showed that the age at presentation (below or equal to 55 years) was significantly higher (73.5%) than that of patients above 55 years (26.5%). The Positive Family history of cancer was also considerably high (34.8%). Although other factors were positive in this group of patients, they were not significantly similar to the percentage worldwide.

Keywords: breast cancer, risk factors, women, incidence.

INTRODUCTION

The leading cause of death due to disease worldwide is cancer, following cardiovascular disease[1]. According to the World Health Organization (WHO), Breast cancer became the most common cancer in females worldwide in 2021, accounting for 12% of all new annual cancer cases worldwide, and became the most commonly diagnosed cancer worldwide, replacing lung cancer[2,3]. According to the reports published on the World Health Organization's official page and GLOBOCAN, it is estimated that its incidence and mortality are constantly increasing. During 2020, there were 2.3 million new breast cancer cases in women and 685,000 deaths[4]. There are notable differences in the incidence and mortality of cancer in females across different regions. The highest reported age-standardized incidence rate was in Australia and New Zealand at 95.5 per 100,000 women, with a relatively low mortality of 12.1. South Central Asia had the lowest incidence at 26.2 but a higher mortality of 13.1. Eastern Asia had the lowest mortality globally at 9.8, despite a moderate incidence of 43.3. These findings highlighted the differences in an attempt to understand effective cancer screening and treatment

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strategies, which may be effective in some regions, and to try to implement them globally[4]. In 2025, new cases were estimated to be 2.45 million, with a mortality of 715,000[5]. In 2030, it is estimated that 307,000 new cases are expected to be diagnosed in women in the U.S., with an estimated death toll of 50,100[6]. While in the Russian Federation, it is estimated that 80,400 new cases of breast cancer are expected to be diagnosed, with a mortality of 23,100[7].

Breast cancer incidence rates are on a constant increase of 0.5% per year. This may be related to the increase in nulliparity, decline in breastfeeding, and the increasing body weights[8]. However, the risk factors leading to breast cancer are still the least understood. There is no single major cause in breast cancer development that makes it difficult to lower its incidence, like lung cancer, where cigarette smoking is considered the leading cause[9]. Stopping cigarette smoking has been proven to lower the incidence of lung cancer. Another example is exposure to the sun in white populations in Australia leads to a high incidence of skin cancers, like basal cell, squamous cell carcinomas, and melanomas[10]. Breast cancer is also difficult to be eradicated by a vaccine similar to Human Papilloma Virus (HPV) vaccines produced mainly for sexually active teenagers to prevent the HPV infection and respectively prevent the metaplasia occurring in cervical and anal lining epithelium leading to cancer[11].

The commonly recognized major risk factors include female sex, age above 50 years, personal history of breast, ovarian, or other cancer, and family history of breast, ovarian, or other cancers. Other less major factors include early menarche, late menopause, nulliparity, late first pregnancy, no or minimal breastfeeding, prolonged use of OCP or post-menopausal HRT, and obesity[12].

This study aims to assess and understand the primary risk factors of breast cancer in Bahrain. To confirm the previous results of the younger age at presentation, and a higher positive family history of breast cancer. Also, to re-evaluate the other well-known risk factors.

MATERIALS AND METHODS

Two hundred twenty-six (226) consecutive breast cancer patients were diagnosed & operated upon by two senior surgeons in the period from August 1999 to August 2020. Their data was entered prospectively in a previously prepared SPSS form. The form included risk factors, presentation, diagnostic approach, staging, and management.

We studied the risk factors: age at diagnosis, early menarche age (11 years and below), and late menopause age (50 years and above). Other factors included parity or nulliparity, late age at first full-term pregnancy (more than 30 yrs.), history of lactation, prolonged history of uninterrupted use of OCP (more than 5 years), prolonged history of uninterrupted use of HRT (more than 2 years), past personal history of breast, ovarian or other cancers, family history of breast, ovarian or other cancers, presence of Diabetes, and weight of patients at presentation. The age at diagnosis was divided twice, each into four categories. The first categorization was less than 35, between 35 and 45, 46 and 55, and above 55. The second categorization was 20 to 29, 30 to 39, 40 to 49, and 50 and above.

Statistical Analysis: SPSS 26 was used for data entry and analysis. Univariate analysis was applied. Frequencies and percentages were computed for the categorical variables. Simple bar charts were used to present the categorical variables.

RESULTS

All patients were females. The first category of Age at presentation showed that those aged less than 35 years were 21 patients (9.3%), 35 to 45 years were 61 patients (27%), and 46 to 55 years were 84 patients (37.2%). The total of those 55 years and below was 166 (73.5%), while those above 55 years were 60 (26.5%) (Figure 1).

The second category of Age at presentation showed that those aged less than 20 years were 0, 20 to 29 years were 4 patients (1.8%), 30 to 39 years were 38 patients (16.8%), and 40 to 49 years were 77 patients (34.1%). 119 patients (52.7%), below 50 years of age, were diagnosed, while those equal to 50 years and above were 107 patients (47.3%) (Figure 2).

Early menarche (11 years and below) was observed in 40 patients (20.2%), and 158 (79.8%) had menarche above the age of 11 years. Those who attained menopause were 97

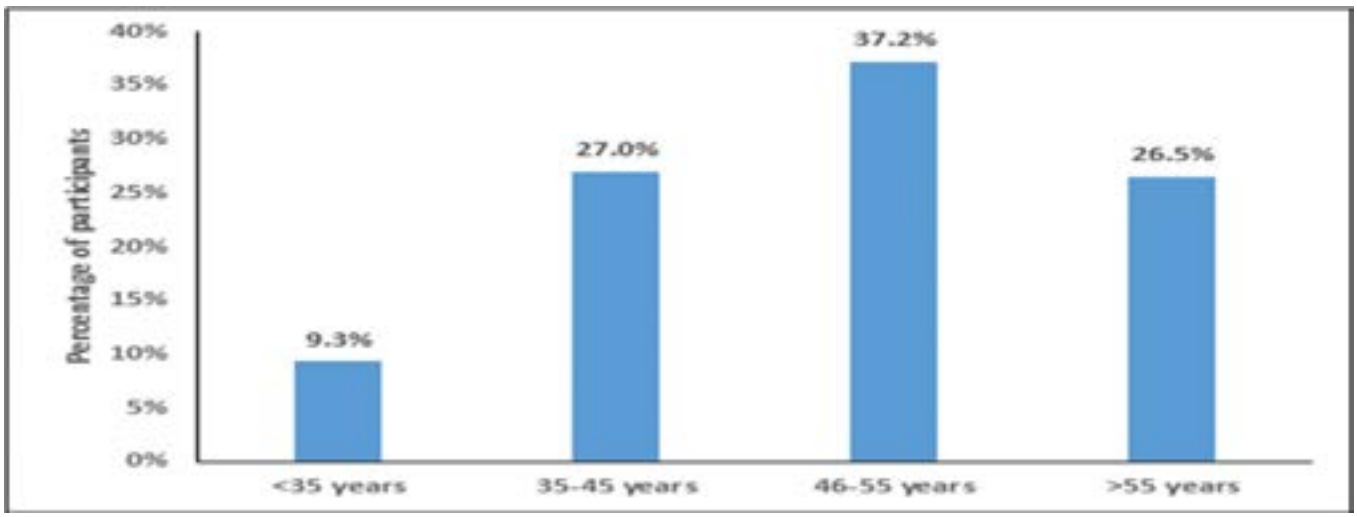

Figure 1. The age of patients at diagnosis was categorized as follows: less than 35 years old 21 patients (9.3%), 35-45 years were 61 patients (27%), 46-55 years were 84 patients (37.2%) and more than 55 years old were 60 patients (26.5%).

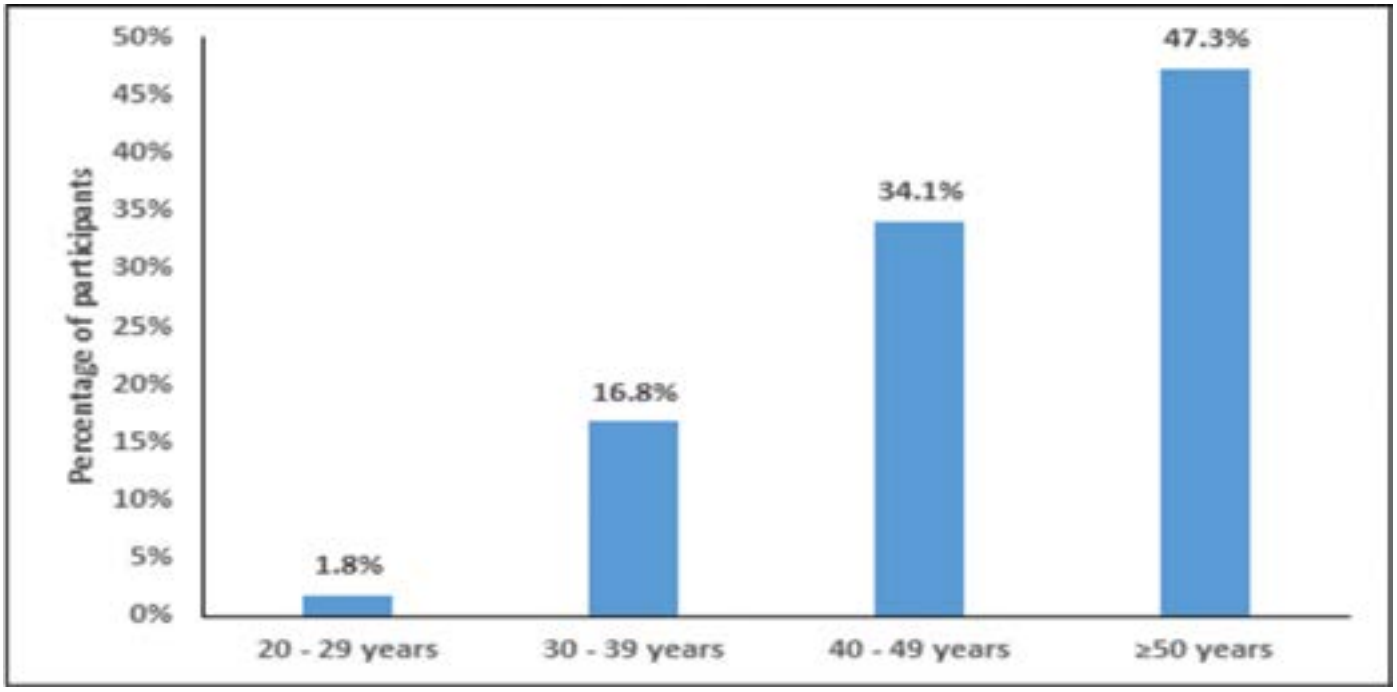

Figure 2. The age between 20 to 29 years (4 patients, 1.8%), age between 30 to 39 years (38 patients, 16.8%), age between 40 to 49 years (77 patients, 34.1%). 119 patients were below 50 years of age.

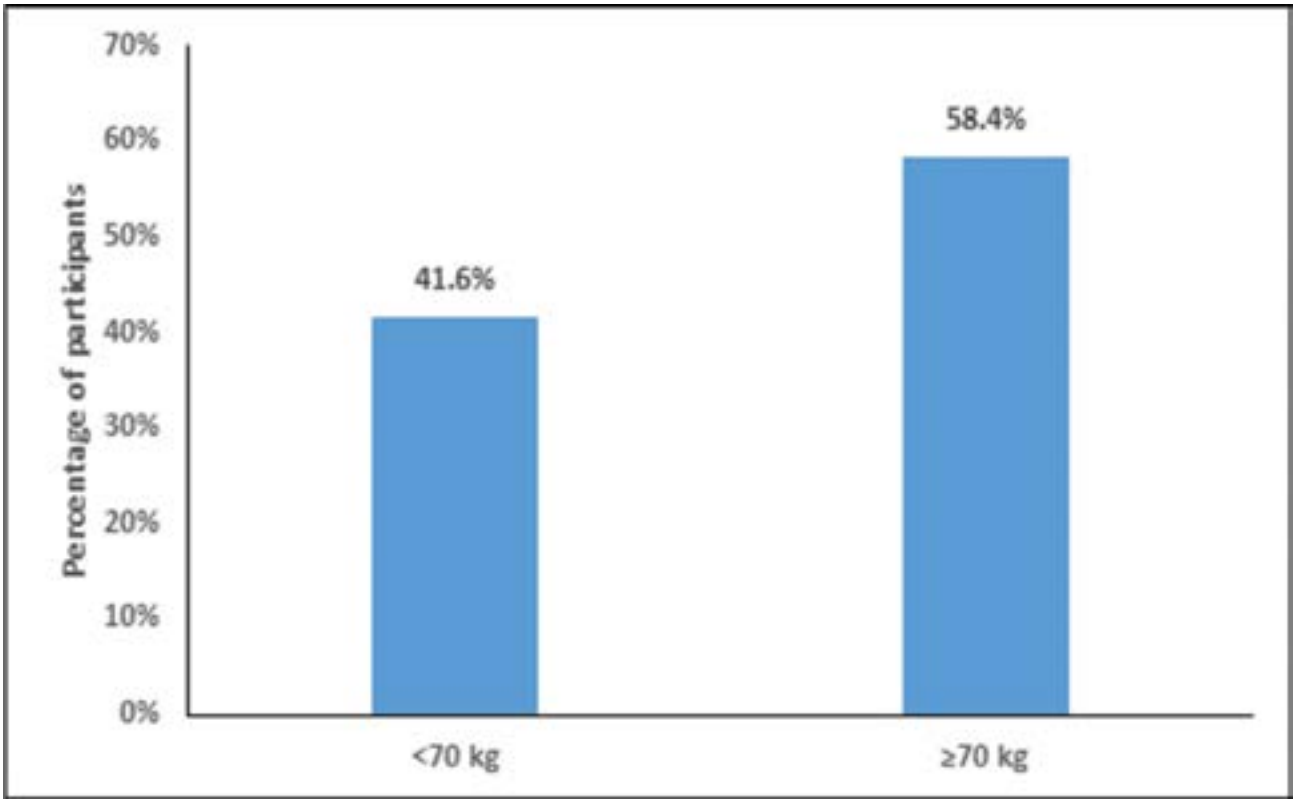

Figure 3. The weight of the patients was at or above the standard adult weight (≥70 Kg) in one hundred twenty-two (58.4%) and was below the standard adult weight (<70 Kg) in 41.6%.

patients (43.1%), and 128 were pre- menopausal (56.9%). Those patients who attained early menopause (age 50 years and below) were 53 patients (63.1%), and only 31 (36.9%) had late menopause (above 50 years). Women who had children (parous) were 179 patients (79.2%), but nulliparous women were only 47 (20.8%). Only 16 patients (8.4%) had their first delivery at more than 30 years of age, while those who had their first delivery at 30 years or less were 154 (81.1%). Lactation history was negative in 62 patients (27.6%) and positive in 163 (72.4%). Only 54 patients (24.5%) used OCP for prolonged periods, while 166 (75.5%) never used OCP. Only 6 patients (2.7%) took HRT, and 216 (97.3%) never used

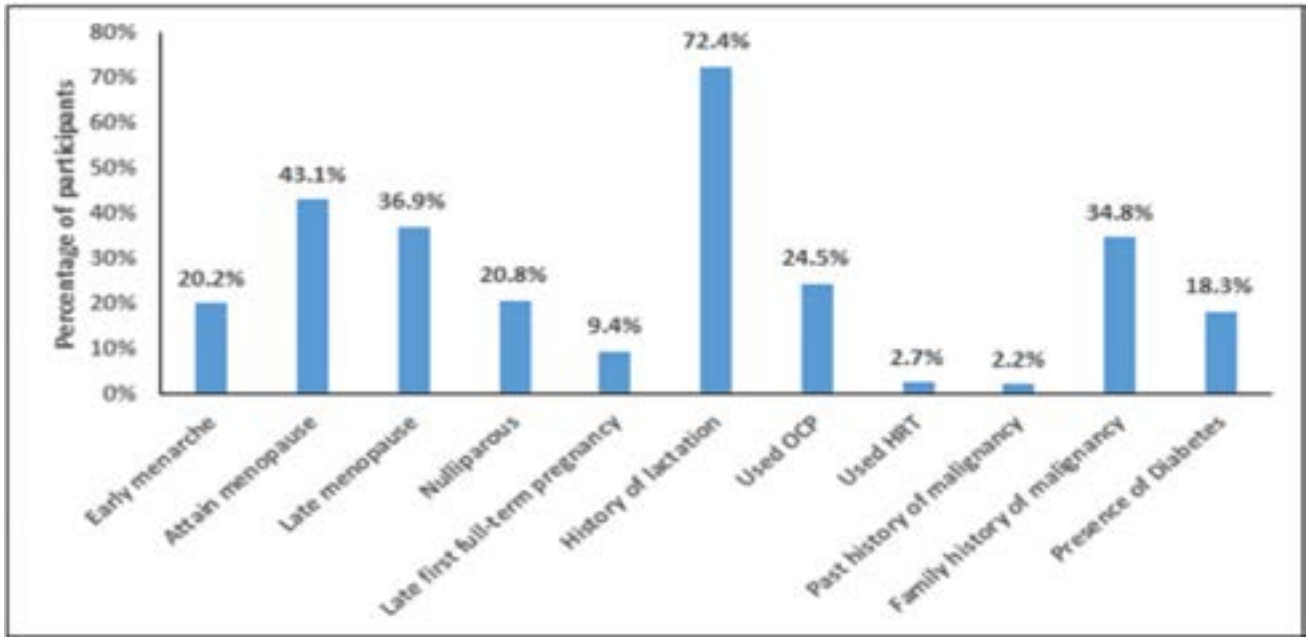

Figure 4. Breast cancer risk factors percentage (%)

HRT. 5 patients (2.2%) had a positive past personal history of malignancy, and 219 (97.8%) had no past personal history of malignancy. Regarding the positive family history of cancer, it was positive in 78 patients (34.8%), whereas 146 (65.2%) had no family history of malignancy. The highest cancer in families with a positive history was breast cancer in 57 patients (73.1%). 5 patients (6.4%) had a positive family history of colon cancer, 2 (2.6%) had ovarian cancer, and 14(17.9%) had other malignancies. 30 patients (18.3%) had Diabetes type II, and the remaining 134 (81.7%) were non- diabetic (Figure 4). The patient's weight was at or above the standard adult weight (70 Kg) in 122 patients (58.4%) and was less than 70 kg in 87 (41.6%) (Table 1 and Figure 3).

DISCUSSION

Breast cancer risk factors are multiple. Some determinants, like being a female, advancing age, or genetic predispositions, cannot be changed. These immutable factors contribute substantially to overall breast cancer risk. Some factors are believed to reduce the risks of breast cancer, such as breastfeeding, age < 20 at first pregnancy, tamoxifen use, prior risk-reduction breast surgery, history of oophorectomy, exercise, and active lifestyle. The Asian, Hispanic, or Pacific Islander race is also believed to have less developed risk factors[13].

Family History: Positive family history is considered a significant risk factor. Some factors that have been found to increase the risk include having one or two relatives with ovarian or breast cancer, having a male relative with breast cancer, having BRCA1 and BRCA2 mutations, having Ataxia-telangiectasia heterozygotes, and having Ashkenazi Jewish ancestry[14].

Worldwide, up to 10% of women diagnosed with breast cancer have both a positive family history and a known genetic predisposition[15]. Individuals who carry either BRCA1 or BRCA2 mutation are at a significantly higher risk for developing breast cancer, and 3-8% of all cases are mainly responsible for breast cancer, and 15-20% of familial cases[16]. "Couch et al" control study suggested that genetic mutations associated with an increased risk of breast cancer were identified in 10.2% of cases of more than 65,000 women with breast cancer[17]. Other factors than genetic mutations or family history that increase the woman's risk of developing breast cancer include the presence of a previous history of breast problems with atypical hyperplasia or lobular carcinoma in situ, and a history of radiation before age 30, especially over the chest[17].

A study done in the Kingdom of Saudi Arabia on breast cancer risk factors among Saudi women showed that the family history of patients with breast cancer was 17.8%, higher than in the participants in the control group (6%)[18]. Results in our study showed a high positive family history of cancer (34.8%) when compared to other nearby or Western figures. It was mainly a positive family history of breast cancer (73.1%). In our previous study in 2009, 20.9% had a positive family history of breast cancer[19]. Both studies support the findings of a higher incidence of family history of breast cancer in Bahrain. This should raise an alarm that there is a genetic predisposition that needs to be disclosed and addressed by higher Bahraini health authorities like how they tackled the problem of sickle cell disease.

Personal History: There is an increased risk of developing cancer in the other breast in women who have already had cancer in one breast. If a woman has a previous history of ductal carcinoma in situ (DCIS), this risk is approximately 5% over the next 10 years. However, if there is also a personal history of an invasive breast cancer, the risk is 1% per year for premenopausal women and 0.5% per year for postmenopausal women[20]. Personal history of cancers such as ovarian, endometrial, and lobular carcinoma in situ (LCIS) is also a risk factor for breast cancer. Benign conditions that can slightly increase the risk of breast cancer include hyperplasia, complex fibroadenoma, radial scar, papillomatosis, sclerosing adenosis, and micro-glandular adenosis.

Table 1. Breast Cancer Risk Factors

	n	(%)
Age at diagnosis		
<35 years	21	9.3
35-45 years	61	27
46-55 years	84	37.2
>55 years	60	26.5
Age at diagnosis		
20 - 29	4	1.8
30 - 39	38	16.8
40 - 49	77	34.1
≥50	107	47.3
Early menarche		
≤11 years	40	20.2
>11 years	158	79.8
Attain menopause		
Yes	97	43.1
No	128	56.9
Age of menopause		
<= 50 years	53	63.1
> 50 years	31	36.9
Had child birth		
Yes	179	79.2
No	47	20.8
Nulliparous		
Yes	47	20.8
No	179	79.2
Late first full-term pregnancy and delivery		
Yes	16	8.4
No	154	81.1
No children	20	10.5
History of lactation		
Yes	163	72.4
No	62	27.6
Used OCP		
Yes	54	24.5
No	166	75.5
Used HRT		
Yes	6	2.7
No	216	97.3
Past history of malignancy		
Yes	5	2.2
No	219	97.8
Family history of malignancy		
Yes	78	34.8
No	146	65.2
Malignancy type in the family		
Breast	57	73.1
Colon	5	6.4
Ovarian	2	2.6
Others	14	17.9
Presence of Diabetes II		
Yes	30	18.3
No	134	81.7
Weight of patient at presentation		
<70 kg	87	41.6
≥70 kg	122	58.4

Our study showed 5 patients (2.2%) with a positive past personal history of malignancy, while our previous study in 2009 showed positive personal history in 1.9%[19]. Therefore, the personal history of malignancy, although not high in our group of patients, is still considered one of the major risk factors.

Being a female is a high-risk factor for developing breast cancer. It is considered that males have an incidence of 1% to develop breast cancer when compared to females, but it is more aggressive in males because of their small-sized breasts, leading to early local and distant metastasis[21]. Women are more prone to develop breast cancer than men because women have more breast cells exposed to the growth- promoting effects of the female hormones estrogen and progesterone[21].

Age: Worldwide, age is found to be a significant risk factor after the female sex factor. The risk of breast cancer increases with age and is two times higher in patients aged more than 50 years as compared to those aged less than 40 years[22]. In 2019, 50% of all new cases of invasive breast cancer occurred in women 50 to 69 years of age[23].

Over 50% of women believe that the risk factors of breast cancer do not increase with age and that "age doesn't matter"[24,25]. With the increase in awareness about breast cancer, women are increasingly attending screening, mainly through health workers in primary care.

Our results showed that the highest age category of females who developed breast cancer was between 46 to 55 years old, 84 patients (37.2%). Followed by the second category, 35-45 years old were 61 patients (27%), more than 55 years old were 60 patients (26.5%), and less than 35 years old were 21 patients (9.3%). In one of our previous studies, the risk factors were examined in 105 breast cancer patients. The study concluded that almost 70% of the patients were 55 years old or younger at presentation[19].

A retrospective study from the United Arab Emirates showed that the incidence in 2021 is highest at the age group between 36-49 years (45.4%), followed by the rest of the groups respectively, 50-64 years were (32.9%), ≤35 years were (12.3%), and ≥65 years were (9.4%)[26]. Emirati patients above 50 years of age at presentation had similar statistics to ours, 45.2% and 47.3%, respectively. This indicates that patients less than 50 years at presentation were 54.8% and 52.7%, respectively.

A study in Malaysia involving 7663 women showed that those aged less than 45 years old were 29.35%[27], while our study was 36.3%. Also in Malaysia, 45-54 years old showed 35.41% while in ours, 37.2%. Age more than 55 years, in Malaysia, was 35.24% while ours was 26.5%. These findings suggest that Malaysia was similar to our result in ages 45-54 years, 35.41% and 37.2% respectively. The overall incidence of ages below 55 years in Malaysia (64.45%) was 10% lower than in Bahrain (73.5%), indicating the younger age group is affected more in Bahrain. In the United States, breast cancer is mainly a disease of the elderly. The median age at diagnosis is 62 years[28]. Approximately 4% are diagnosed in women younger than 40, and 16% in women under 50 years of age[29,30]. In contrast, data from Russia shows increasing age-standardized incidence rates from 33 to 47 per 100,000 between 1993 and 2013[31], with mortality rates rising from 11.5 per 100,000 in 1963 to 39.8 in 2002[32], though specific age at presentation data is limited in English- language literature. In contrast, Middle Eastern countries demonstrate similar patterns to our results, with breast cancer presenting at significantly younger ages. In Iraq, breast cancer affects women younger than 50

years in 45%, and 25% are younger than 45 years[33]. The mean age at presentation in Iraq is 48 years, with a median of 47 years. Others reported a peak age at 35 to 39 years[34]. Similarly, in Iran, the mean age at diagnosis is 47 years[35]. The peak age in Iran occurs at 45 to 49 years (15.8% of cases)[36], and researchers note that breast cancer diagnosis in Iran occurs approximately a decade earlier than in most developed countries[35,37]. Other factors, which have been shown to play an important role in other studies, are:

Early menarche and late menopause: Early age of menarche (11 years and below) is considered a risk factor because breast tissue proliferation is stimulated by exposure to estrogen and progesterone hormones[38,39]. Breast cancer risk is about 20% higher among those who begin menstruating before age 11 compared to those who begin at age 14 or older[40]. There is a 10% reduction in breast cancer risk for each 2-year delay in menarche[40]. Results from our study showed that 40 patients (20.2%) had early menarche. In our previous study, the average age of menarche was 12.7 years, and the early menarche was only in 20 patients (19.6%) (25). Early menarche may not be sufficiently significant in our patients.

Women who experience menopause at age 55 or older have about a 12% higher risk compared to those who do so between ages 50-54[40]. Late menopause is a significant risk factor for breast cancer in many studies. According to the Australasian Menopause Society, the average menopausal age is 51 years. The American Society of Clinical Oncology confirmed that delayed menopause increases the risk of developing breast, uterine, and ovarian cancer as it exposes women to more hormones, such as estrogen. A publication in Lancet Oncology, on more than 400,000 women, showed that for every year older a woman was at menopause, there was an increased risk of breast cancer by approximately 3%[40]. The risk doubles with menopause after age 55. Our study showed that most of our patients are pre-menopausal (56.9%), and only 43.1% attained menopause. Those who attained late menopause were only 36.9%. In our previous study, late menopause was in three patients only (2.8%), with an average age of 51 years for women going through menopause[19]. This factor may also not be sufficiently significant as more than half of our patients were pre-menopausal.

Other factors: Nulliparous women, with late first pregnancy (after 30 years of age), who never breastfed, who use HRT for various reasons, are at increased risk of developing breast cancer compared to women who are not[41,42,43]. These factors are associated with an increased risk of breast cancer globally. On the contrary, parous women with multiple pregnancies and/or who became pregnant at an early age have a reduced breast cancer risk[44,45]. In this study, 20% of our patients were Nulliparous, almost similar to our previous study that showed 19%[24].

Most of our patients had their first pregnancy at less than 30 years (81.1%), only 8.4% had late first pregnancy at an age more than 30 years. The previous data showed that most of the patients were married and had children at an early age[19]. 81% of the patients were parous, and 75.2% of them had their first pregnancy at an early age (less than 30 years)[19]. This factor may also not be sufficiently significant in our patients.
In a review of 47 epidemiological studies in 30 countries on the effect of breastfeeding on the risk of breast cancer, it was found to reduce the risk by 4% for every 12 months of breastfeeding. Therefore, the longer women breastfeed, the more they are protected against breast cancer[46,47].

In this study, Lactation history was positive in more than two-thirds of our patients, while only 27.6% never breastfed, similar to our previous study, where three-quarters of the patients had a positive history of lactation[19]. Oral contraceptive pills were used uninterrupted in 24.5% of patients. Only 2.7% of the patients were on HRT. Our previous study showed that 20% used OCP and 1.9% used HRT[19].

A meta-analysis of 58 international studies in the United Kingdom, including 568,859 women and 143,887 breast cancer cases, concluded that HRT use for 5 years daily is associated with increased breast cancer risk starting at age 50. The increase is 2 per 100 women (1/50 women)[48]. HRT use increases breast cancer risk amongst women in the general population, and more in women with positive family history to familial cancer[49,50]. In our study, the number of patients taking OCP or HRT is too low to draw any conclusions.

Diabetes: Many studies suggest that people with diabetes have a significantly higher risk of breast cancer incidence than non-diabetic individuals[51,52]. A population-based study to determine the impact of diabetes on breast cancer treatments and outcomes, and women without diabetes, showed that breast cancer-specific mortality remains higher among diabetic women or those with preexisting cardiovascular disease[53]. Some studies also showed that hyperinsulinemia in type II diabetics may promote mammary carcinogenesis. Insulin resistance has been linked to an increased risk of breast cancer[54,55]. As such, it was found that 33.6% of breast cancer cases from the Kingdom of Saudi Arabia were Diabetic[18]. Diabetes in our group of breast cancer patients was only 18.35%.

Obesity: It is a recognized risk factor for the development of breast cancer and is associated with an increased risk of postmenopausal estrogen receptor-positive breast cancer and worse cancer-related outcomes for all breast tumor subtypes[56]. Studies have shown constant associations between obesity and the development of different types of malignancies with poor prognosis, including breast cancer[57]. Several factors contribute to the obesity-cancer link, like altered levels of steroid hormones, insulin and insulin-like growth factors, adipokines, changes in the microbiome, and local and systemic inflammation[58]. A recent meta-analysis noted that obese women with breast cancer have 11% decrease in overall survival rate, regardless of menopausal status[59]. Another reported that the risk of postmenopausal breast cancer increases by 11% for every 5 kilograms gained during adulthood[60].

Increased body mass index after menopause and weight gain throughout adult life after the age of 20 are associated with increased risk of postmenopausal breast cancer[61]. While higher weight during adolescence and early adulthood (age 30 years and under) is observed to have an inverse effect[62].

Many studies have shown that obese breast cancer patients develop more postoperative or other treatment complications compared to non-obese women. Furthermore, they have an increased risk for local recurrence. Even systemic

chemotherapy and endocrine therapy are less effective. Aromatase inhibitors may also be selectively less effective than tamoxifen. Obese women may also have more surgical complications on breast reconstruction[63]. In our study, we had only 18.3% Diabetics but 58.4% were overweight (at or above the standard adult weight (70 Kg).

CONCLUSIONS

Breast cancer patients studied still show a younger age at presentation. Those below or equal to 55 years of age were affected significantly higher (73.5%) than the similar group in the United States or other Western countries. Other countries in the Middle East have similar results to ours.

Positive Family history for cancer was also significantly high (34.8%), while the international figures do not exceed 5-10%. Although familial breast cancer showed that it is common in Bahrain, more studies are required to support and understand the reason for developing breast cancer at an early age.

Other risk factors were not sufficiently significant when compared to the worldwide. This could be due to the small number of patients studied, or it could be that our breast cancer patients have still-unstudied or unknown risk factors. More studies on other factors in the kingdom are needed. We would recommend that strict breast screening programs in the Kingdom of Bahrain start at the age of 40 years and in positive families at an earlier age.

We would also encourage high-risk women, especially first-degree relatives of patients with breast cancer, to perform genetic testing and consider prophylactic surgeries.

Authorship Contribution: Kameela Sayed Husain Ali Husain Majed, Analysed statistical data in SPSS and data curation, writing the original manuscript; and main corresponding Author. Suhair Khalifa Al-Saad, Data collected prospectively in SPSS , developed the research thesis ,design and writing the original manuscript. Fatima Al Shenawi, Assisted in Data collection. Hamdi Al Shinawi, supervision, review and approval of the final version of the manuscript;

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