



## Breast Cancer in Muslim Countries: Risk Reduction Strategies

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### Authors' contributions

*This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.*

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### ABSTRACT

Breast cancer is the most common cancer in women in western countries and is becoming significant in many developing countries. It is the most common cancer and the primary cause of cancer-related mortality in women in Muslim countries. The incidence of breast cancer ranges from low of 20.4 to high of 78.7 cases per 100,000 in Tajikistan and Lebanon, respectively. The mortality ranges from 8.7 to 25.9 cases per 100,000 in Libya and Nigeria, respectively. The incidence in Muslim countries is low compared to the incidence in US which is at 92.9 cases per 100,000, according to World Health Organization (WHO) data from 2012. However, mortality in US remains low at 14.9 cases due to early detection and better treatment. Breast cancer incidence is increasing in Muslim countries. Greater number of patients present at a younger age and a later stage as compared to the western countries. The major risk factors increasing the incidence of breast cancer include dietary habits, physical activity, weight, reproductive patterns, breast feeding, and supplemental hormone use. A significant decrease in the incidence and mortality in Muslim countries can be achieved by a program incorporating simple risk reduction measures, early detection strategies and specific medical intervention in high-risk women. This will require a cooperative effort of the community, physicians and government.

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## 1. INTRODUCTION

More than one million women worldwide are diagnosed with breast cancer each year. In western countries, it is the most common cancer and is becoming significant in many developing countries [1,2]. It is the leading cause of cancer-related mortality (14.7%) in females, accounting for 522,000 deaths each year [3]. Developed countries early detection programs and optimal treatments have reduced the mortality substantially even though the incidence is high. However, Muslim countries with limited resources, no organized early detection programs and inadequate treatments have very high mortality even though the total incidence is lower than in western countries. Cancer in general and breast cancer specifically, is potentially a preventable disease, and also amenable to early detection which can frequently lead to a cure [4]. Many of the countries in Muslim world have limited resources which is evident by the increasing number of breast

cancer incidence in those countries [5]. Treating advanced disease is expensive and not very effective [6]. Muslim countries could more fruitfully direct their efforts at prevention and screening rather than the much more expensive and complicated treatment of advanced disease [4]. A previous review of breast cancer in Muslim countries recommended specific measures for reducing the risk and mortality. The present article updates the information including the most recent statistics from WHO's GLOBOCAN 2012 database. It also incorporates newer risk reduction medications.

## 2. INCIDENCE AND MORTALITY OF BREAST CANCER IN MUSLIM COUNTRIES

The incidence of breast cancer in the various Muslim countries is presented in Fig. 1. The data is derived from the WHO's GLOBOCAN 2012 database [7]. It includes information up to 2012. More recent data suggests increasing rates [3].

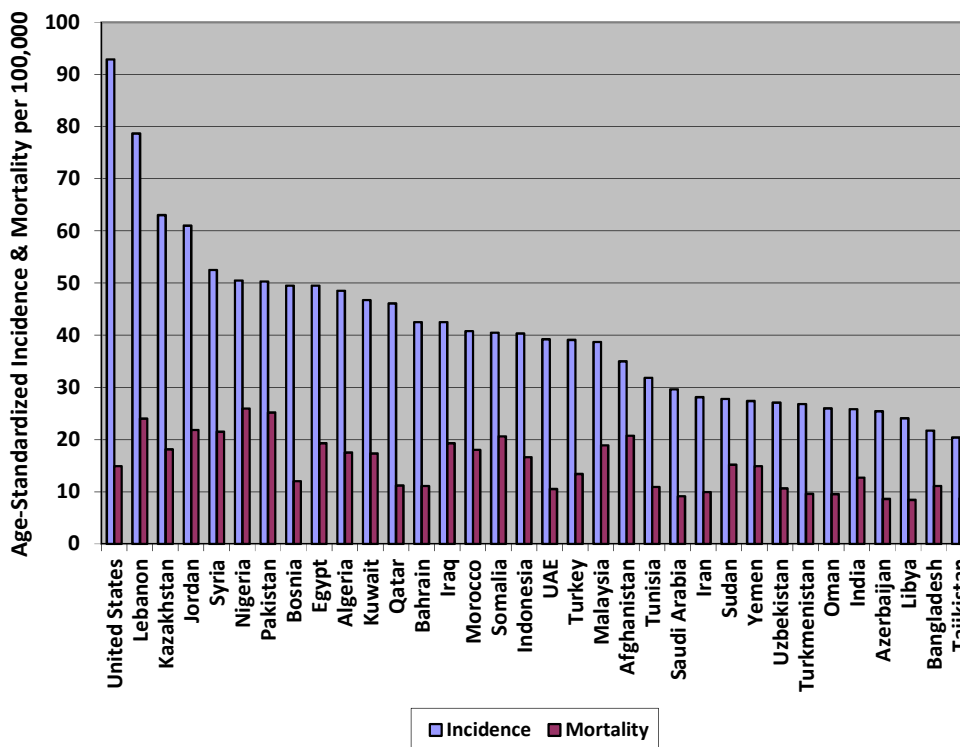


Fig. 1. The incidence and mortality of breast cancer through 2012 in Muslim countries and US; WHO's GLOBOCAN 2012 database [7]

Muslim countries in general have a low incidence as compared to the Western world, which is probably related to multiple factors including low socioeconomic status, shorter life expectancy, and favorable reproductive patterns. On the other hand, it has significantly increased since the last data reported by WHO GLOBOCAN 2002 database. Muslim countries with high incidence includes Lebanon, Kazakhstan and Jordan with rates of 78.7, 63, and 61 per 100,000, respectively. Muslim countries with a low incidence includes Tajikistan, Bangladesh and Libya with rates of 20.4, 21.7, and 24.1 per 100,000, respectively.

### **3. RISK FACTORS FOR BREAST CANCER**

There are number of causes for breast cancer that includes combination of genetic, environmental and lifestyle factors. Developing strategies to prevent or minimize risk require an understanding of potential causative factors. The data identifying the risk factors is predominantly based from evaluating the risk of breast cancer in people migrating from low risk countries to the west. They acquire the risk of their adopted country indicating that lifestyle factors are the major drivers rather than generic factors [8]. This observation clearly suggests that lifestyle and socio-economic factors are a major source of etiology of breast cancer. The various risk factors are discussed in further detail, as follows.

#### **3.1 Hormonal and Reproductive Characteristics**

Breast cancer is a hormonally dependent cancer and a woman's menstrual and reproductive history modulates the risk. Specifically, early age at menarche and late age at menopause increase risk, whereas early age at first pregnancy and multi-parity decrease the risk [9].

##### **3.1.1 Menstrual history**

Evidence indicates that the onset of menstrual cycles before the age of 12 is associated with a higher risk for developing both pre- and postmenopausal breast cancer [10]. A shorter menstrual cycle from age 20-39 is reported to increase the risk of breast cancer [8]. The possible explanation could be the longer time spent in the luteal phase, with elevated estrogen and progesterone levels [4]. In contrast, irregular

cycles and longer gap between menstrual cycles appears to lower the risk [11].

Women with late age at menopause are at significantly higher risk of breast cancer. This is probably due to the greater lifetime exposure to endogenous hormones. Menopause occurring beyond the age of 45 increases the risk of breast cancer by approximately 3% per year. This is because of continued proliferation of the ductal epithelium from extended exposure to endogenous hormones [4].

##### **3.1.2 Pregnancy and lactation factors**

Multi parity (>3 children) was a significant protective factor of breast cancer [12]. In general, women who has given birth have a lower risk of breast cancer than a woman who has never produced an offspring. A preponderance of the studies report decreased risk with a first full-term pregnancy at a younger age [4,7]. This is probably related to the maturation of glandular epithelium of the mammary cells, which occurs in the first pregnancy [13].

It was observed as early as 1926, that women who never lactated were more susceptible of developing breast malignancy [14]. A majority of case control and cohort studies report a reduction in the risk with a longer duration of breast-feeding [4]. The magnitude of risk reduction has varied substantially from study to study. The most favorable studies report at least a 50% reduction in the risk with breast feeding each child for two years or longer [15].

##### **3.1.3 Exogenous hormonal influence**

Exposure to exogenous hormones as oral contraceptives and hormone replacement therapy result in an increase in the risk of breast cancer [16]. Multiple studies have established that oral contraceptives do not increase the risk of breast cancer [17]. However, use of oral contraceptives in teenage years and before first full-term pregnancy may result in a modest increase [4,18].

The landmark Women's Health Initiative study of more than 16,000 women in the U.S., provided strong evidence that combined estrogen and progestin replacement in postmenopausal women lead to a 26% increase in the risk of breast cancer [4,19].

### 3.2 Inherited Genetic Mutations

Breast cancer genes (BRCA1 and BRCA2) are human genes that produce tumor suppressor proteins. Inherited mutations in the BRCA1 and BRCA2 genes confer a greatly increased risk of breast cancer, with individual lifetime risk estimates ranging from 26 to 85 percent [20]. These mutations, however, are present in a small proportion of all women with breast cancer (5 to 10%) and do not account for the majority of cases among women with breast cancer in a first-degree relative. The incidence of BRCA1 and BRCA2 among women in Muslim countries is limited. Reports from Turkey and Pakistan based on small number of samples suggest that the incidence is similar to the western countries [4,21].

### 3.3 Personal or Family History

A family history of breast cancer or the presence of breast cancer genes (BRCA 1 or BRCA 2) confer a high risk for an individual [4]. Family history considerably increases the risk. The risk is increased almost six-fold, if two or more first-degree relatives had breast cancer or a family member had bilateral breast cancers [22].

### 3.4 Role of Diet and Exercise

Nutritional factors have been extensively evaluated to account for the varying incidence of breast cancer across the world. The predominant role of diet as a causative factor has been advanced as a hypothesis to explain the increase in the risk of migrant populations. However, this has been difficult to study and prove a direct relationship between the two [4]. The difficulty in proving this may be because of a complex interaction between diet and weight. Women who gain weight after the age 18 have a higher risk for developing postmenopausal breast cancer [4,23]. Risk of relapse following the treatment of breast cancer decreases when women either lose weight or at least do not gain weight [4,24].

Almost all studies involving breast cancer and alcohol consumption report an increase in the risk even with the modest intake of alcohol [4,25,26].

Regular physical activity is associated with decreased risk as evidenced by data from both prospective and retrospective studies [4,27]. This may be related to lower weight in women who

exercise regularly. Girls who participate in vigorous physical activity before the onset of menarche have a significant reduction in the risk of breast cancer. This may be related to the delay in the onset of ovulatory cycles, thus decreasing lifetime exposure to estrogens [4,28]. Physical activity also seems to be beneficial in women diagnosed with breast cancer as it decreases the risk of relapse [24].

### 3.5 Breast Tissue Density

Women with dense breast tissue are at moderately increased risk for breast cancer [29]. Besides the increased risk, women with dense breast also experience a delay in diagnosis, as their tumors are difficult to detect on routine mammograms. Increased breast density on mammograms is associated with decreased sensitivity and specificity [30].

Table 1 summarizes the risk factors [31].

## 4. RISK ASSESSMENT

Estimating an individual's risk is necessary to identify those who are at higher risk and may benefit from reduction strategies. There are two models available to the clinician to estimate an individual's risk. These models incorporate various risk factors to provide a proportionate risk number which can be utilized to separate women with low risk from those with higher risk. A commonly used tool is the Gail model. It is derived from data of U.S. cancer registries. It incorporates age, race, age at menarche, age at first live birth, first degree relatives with breast cancer, previous breast biopsies, and atypical hyperplasia on any previous breast biopsy [4,32]. The model compares a variety of risk factors to evaluate the risk of a given person to the average American. A 1.67 fold higher 5-year cumulative risk than normal is defined as high risk. It has not been tested in non U.S. populations. It does not assign significant value to family history. Another tool, the Claus model places more emphasis on family history of breast cancer and as such is more appropriate for people with family history of breast cancer [4,33].

## 5. BIOLOGY OF BREAST CANCER

The working model of evolution of breast cancer suggests that a normal cell undergoes hyperplasia, subsequently to atypical hyperplasia. Later it progresses to *in situ* cancer.

**Table 1. Breast cancer: Relative Risk with various causative factors [4]**

<b>Risk factors</b>	<b>Relative risk</b>
Physical activity [33] - Inactivity vs. regular activity	1.25 - 1.4
Age at menarche [10] - <12 years vs. >15 years	1.3
Obesity [23,24] - BMI $\geq$ 25 kg/m <sup>2</sup> vs. BMI <25 kg/m <sup>2</sup>	1.3 - 2.1
Alcohol use [25] - >3 drinks per day vs. no drinks	1.46
Combined postmenopausal hormone replacement therapy [19] - Current use or at least 5 years of use vs. No use	1.6
Age at first live birth [10] - >30 years or nullparity vs. <18 years	1.9
Age at menopause [12] - >55 years vs. <45 years	2.0
Mammographic density [28] - Dense breast tissue vs. little or no density	4.0 - 6.0
Age [28] - >65 years vs. <65 years	5.8
Proliferative breast disease [28]	
- Hyperplasia without atypia	1.5 - 2.0
- Atypical ductal hyperplasia	4.0 - 5.0
- Atypical lobular hyperplasia	4.0 - 5.0
Non invasive breast cancer [28]	
- Lobular carcinoma <i>in situ</i>	4.0 - 10.0
- Ductal carcinoma <i>in situ</i>	8.0 - 10.0

The *in situ* cancer eventually develops into an invasive cancer [4]. It becomes mammographically recognizable at 1 mm and palpable at 1 cm. This progression of events from a normal cell to the clinically detectable cancer happens over several years [4,34]. This prolonged duration affords ample opportunities to intervene and prevent the development of invasive disease.

## 6. STRATEGIES FOR RISK REDUCTION

The pathophysiology and the gradual evolution of this disease make it an ideal situation for intervention at different stages to halt its progression to invasive cancer. Maintaining ideal body weight by proper diet, physical activity, avoiding alcohol and breast feeding are general risk reduction approaches, relatively easily applicable to all women. These simple measures could reduce the risk by as much as 40% [4]. Additional risk reduction strategies for high risk populations include increased screening, medications and surgical procedures. Physicians should focus on advising patients and families about risk reduction strategies specially for those with high risk with regular clinic visits. Women with family history are ideally handled by high risk clinics which can provide genetic counselling appropriate genetic testing like BRCA1 & BRCA2 and makes specific recommendations on a case by case basis. These measures can include general risk

reduction strategies to more specific interventions like medications and prophylactic mastectomy.

### 6.1 Physical Activity

Physical activity has a beneficial effect by reducing the risk based on the available published data [4]. There are several studies that have shown a consistent pattern of risk reduction, including prospective studies [35]. A more recent review of 73 observational studies indicated that the breast cancer risk can be reduced by approximately 25% in women with moderate to vigorous physical activity compared with inactive women [36,37].

### 6.2 Diet

The role of specific dietary factors as a means of reducing the risk of breast cancer remains unsupported. Prospective studies have not conclusively provided evidence to suggest a major role of dietary fat in the etiology of breast cancer. However, women who gain weight in the middle age years have a higher risk of developing breast cancer. Current data supports minimizing weight gain in adult years decreases the risk [4,24]. Strong observational data indicate that weight gain in the premenopausal period and being overweight or obese after menopause increase breast cancer risk [38,39]. Avoiding alcohol intake reduces the risk [24,25]. It is estimated that breast cancer risk is increased by

7% to 10% for each one-unit increase in intake of alcohol per day [40].

### 6.3 Breast Self Examination

Breast self examination (BSE) is a simple tool, however, scientific data has not consistently shown that it decreases breast cancer mortality [4]. BSE correlates with an earlier clinical stage which has better prognosis and as such could be a valuable tool in countries with limited medical resources lacking more sophisticated screening methodologies [41].

### 6.4 Clinical Breast Exam

Mammographic screening misses about 15% of the cancers which are detectable by a clinical breast exam (CBE) [4]. The percentages are even higher in younger women. Either a regular clinical examination or, depending upon the resources of the countries, in combination with mammography, will optimize early detection [4,42].

### 6.5 Mammography

Multiple randomized trials have shown that mammography reduces mortality by 30% with

annual or biennial screening in women aged 50 to 69 years. In women younger than 50 years randomized trial data has not consistently shown a reduction in mortality. This could be related to small number of women screened and other limitations of study design [4,43].

### 6.6 Medications for Risk Reduction

Tamoxifen and Raloxifene are two selective estrogen receptor modulators (SERMs) that have demonstrated efficacy in large randomized trials for breast cancer prevention. The population studied were women aged 35 years or older, with a Gail model risk of more than 1.67 [4,44,45]. Aggregate data from four studies using this approach showed a 38% risk reduction [4,46].

The current recommendations are for women over 35 years of age who fall in the high risk category by Gail model consider taking Tamoxifen for 5 years [4].

A second generation SERM, Raloxifene, is equally effective as Tamoxifen in reducing the risk, in a randomized trial of almost 20,000 women. Raloxifene, has a better side effect profile than Tamoxifen and may be considered the preferred drug of the two [4,47].

**Table 2. Breast cancer: Lifestyle changes for risk reduction [4]**

Types of intervention	Mechanism of action	Specific approach	Relative risk reduction
Childbearing patterns (first live birth under 18 vs. over 30 or nulliparity)	Early pregnancy causes terminal differentiation of ductal epithelium	Pregnancy and prenatal education	40%
Avoidance of hormone supplements	Adipose tissue stores hormones	Physician education	26%
Postmenopausal weight management		Community education improving access to physical fitness facilities	20 - 30%
Healthy dietary habits	Lowers body fat, enhances immune function, affects hormone levels and delays menarche	Community education: legislation requiring food labeling, controlling school lunch menu	20 - 30%
Physical activity		Individual: exercise/education, planned/mandatory exercise programs	20 - 30%
Breast feeding	Maturation of ductal epithelium	Nursing Education/providing privacy at work places for nursing mothers	4% reduction for every 12 months of breast feeding

**Table 3. Breast cancer: Risk based recommended interventions [4]**

	<b>Risk status</b>	<b>Management</b>
Average risk	5 years Gail model risk < 1.67%	<ul style="list-style-type: none"> <li>• Yearly clinical breast exam</li> <li>• Yearly mammographic screening (beginning at age 40 years)</li> <li>• Breast self-examination</li> <li>• Recalculate risk every 3 years</li> </ul>
High risk	5 years Gail model risk > 1.67%	<ul style="list-style-type: none"> <li>• Clinical breast exam at interval of every 6-12 months</li> <li>• Yearly mammographic screening (beginning at age 40 years)</li> <li>• Breast self-examination</li> <li>• Consider tamoxifen or raloxifene</li> </ul>
High risk	Prior thoracic radiation therapy	<ul style="list-style-type: none"> <li>• Clinical breast exam at interval of every 6-12 months</li> <li>• Yearly mammographic screening (beginning 8-10 years after radiation therapy or at age 40, whichever is first)</li> <li>• Breast self-examination</li> <li>• Consider tamoxifen – (data supporting the benefit of tamoxifen is limited in women who had thoracic irradiation and those who have BRCA1 and BRCA2 mutations.)</li> </ul>
High risk	Atypical lobular or ductal hyperplasia	<ul style="list-style-type: none"> <li>• Clinical breast examination every 6-12 months</li> <li>• Yearly mammographic screening</li> <li>• Breast self-examination</li> <li>• Consider tamoxifen or raloxifene (Maximum reduction of risk in women with atypical hyperplasia.)</li> <li>• Consider Aromatase Inhibitors in postmenopausal women</li> </ul>
	Strong family history or known genetic predisposition	<ul style="list-style-type: none"> <li>• Clinical breast examination every 6-12 months</li> <li>• Yearly mammographic screening (beginning at age 25 or 5-10 years before earliest index case)</li> <li>• Breast self-examination</li> <li>• Consider tamoxifen - (data supporting the benefit of tamoxifen is limited in women who have BRCA1 and BRCA2 mutations.)</li> <li>• Consider prophylactic mastectomy</li> <li>• Consider prophylactic oophorectomy</li> <li>• Consider Aromatase Inhibitors in post menopausal women</li> </ul>

Aromatase Inhibitors also substantially reduce the risk of Breast cancer in high risk women, but these are indicated in postmenopausal women [48]. Premenopausal women who receive ovarian suppression may now benefit from an aromatase inhibitor as well, a class of drugs that until now has been recommended only for postmenopausal women [49].

### 6.7 Bilateral total mastectomy

Bilateral total mastectomy in women with BRCA1 or BRCA2 mutation can have significant

reduction in the risk of breast cancer, as reported by two small prospective studies [4,50,51]. Retrospective studies with long follow up of 13 to 14 years in women with BRCA1 and BRCA2 treated with bilateral mastectomy had a 90% reduction in the risk [4,52,53].

### 6.8 Bilateral Salpingo-oophorectomy

In women with BRCA1 and BRCA2 mutations, bilateral salpingo-oophorectomy at or before the age of 40 results in an approximate 40% reduction in the risk of breast cancer [4,54].

These mutations also increase the risk of ovarian cancer; however, it is a much lower risk than breast cancer. A salpingo-oophorectomy would decrease the risk of both ovarian and breast cancer [4].

Table 2 summarizes general measures of breast cancer prevention [4]. Table 3 identifies appropriate medical management based on risk status [4,55,56].

## 7. CONCLUSION

Muslim countries are witnessing an increasing burden of breast cancer. The slow clinical evolution of breast cancer from normal cells make it suitable for prevention measures. Their limited resources can be better utilized in prevention strategies than treating advanced cancer which is not only more expensive but less successful. The goal should be to shift the focus of the countries from treatment of an advanced disease to risk reduction and early detection approaches. Simple strategies of dietary changes, regular exercise, weight management combined with regular screening, can significantly reduce the risk and mortality from breast cancer. Society should make vigorous efforts to educate and remove the stigma associated with a disease so women can seek assistance freely. This will require a joint effort by physicians, community, government and non-profit institutions.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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