

Review Article

Breast Cancer Incidence and Risk Reduction with Special Reference to Muslim Countries

Nureen Haq, BBA, MS II; Mohamed M Haq, MD;

Abida Haque, MD¹

¹Professor of Pathology

Weill Medical School of Cornell University

New York, New York

and Attending Pathologist

The Methodist Hospital

Houston, Texas

Abstract

Breast cancer is the leading cause of cancer-related mortality in women in the Muslim world. The incidence of breast cancer ranges from highs of 58.9, 52, and 50.1 cases per 100,000 in Bosnia, Lebanon, and Pakistan, respectively, to a low of 13.2 in Oman, according to World Health Organization (WHO) data from 2000. Breast cancer incidence is increasing in Muslim countries, while also presenting in patients at a younger age and in a more advanced stage. The major factors affecting the incidence of breast cancer — diet, exercise, weight, reproductive patterns, breast feeding, and supplemental hormone use — are lifestyle choices that can be modified. A campaign to introduce simple risk reduction and early detection strategies, as well as specific medical intervention in high-risk women, can help significantly decrease the incidence and mortality. This requires a joint effort by physicians, government institutions, and the community to allow every Muslim woman the best chance for survival.

Key words: Islam, breast cancer, prevention and control.

Cancer is a leading cause of mortality worldwide, accounting for 13% of all deaths. In 2005, 7.6 million people died from cancer, and mortality is projected to increase over the next 10 years, reaching 9 million in 2015 and 11.4 million by 2030. More than one million women worldwide are diagnosed with breast cancer each year. It is the leading

cause of cancer-related mortality in females, accounting for 375,000 deaths each year.¹ A majority of the deaths are in low- and middle-income countries where the disease is frequently diagnosed late and treated suboptimally. In the developed countries, the mortality rate of women with breast cancer is low, while in developing countries, a majority of those with breast cancer will die from it.² The incidence of breast cancer is increasing in Muslim countries.³ Cancer in general and breast cancer specifically, is potentially a preventable disease with early detection frequently leading to a cure. The Muslim world is large with many of its countries having lim-

Abida Haque, MD
Professor, Department of Pathology
San Jacinto Methodist Hospital
4401 Garth Road
Baytown, Texas 77521

ited resources. Their efforts could be more fruitfully directed at prevention and screening rather than the much more expensive and complicated treatment of advanced disease.

Incidence of Breast Cancer in Muslim Countries

Figure 1 presents the incidence of breast cancer in the various Muslim countries. The data is derived from the WHO's GLOBOCAN 2002 database.⁴ It includes information up to 2000. More recent data suggests increasing rates.³ 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. However, the incidence of breast cancer in the Muslim countries of Bosnia, Lebanon, and Pakistan is high with rates of 58.9, 52, and 50.1 per 100,000, respectively. This may be related to a better socioeconomic status in Bosnia and Lebanon. The reasons for a higher incidence in Pakistan are not clear, although they may be driven by genetic factors. The incidence of BRCA1 and BRCA2 mutations are reported to be similar to that in the Western world.⁵ Muslim countries with a low incidence include Oman, Tajikistan, and Bangladesh with rates of 13.2, 13.2, and 16.6 per 100,000, respectively.

Risk Factors for Development of Breast Cancer

Epidemiological studies defining risk factors for breast cancer have been conducted in Western countries. Women who migrate to countries of higher incidence subsequently acquire the prevailing risk of breast cancer in their new country.⁶ An increase in risk can manifest in the same generation or in subsequent generations, depending on the age at migration. This observation strongly suggests that lifestyle or socioeconomic conditions rather than genetic factors play a major role in the development of breast cancer. Developing strategies to prevent or minimize risk require an understanding of potential causative factors. These factors can be classified into the following:

1. Reproductive factors

Age at Menarche

A preponderance of evidence indicates that the onset of menstrual cycles before the age of 12 is asso-

ciated with a higher risk for developing breast cancer.⁷ The increased risk is evident in both pre- and postmenopausal breast cancer. This phenomenon may be related to greater lifetime exposure to endogenous hormones.

Menstrual Cycle Characteristics

A few studies suggest a shorter menstrual cycle from age 20-39 is associated with higher risk.⁷ This may be a result of a greater amount of time spent in the luteal phase, where estrogen and progesterone levels are elevated. Conversely, long duration between menstrual cycles and irregular cycles are associated with lower risk.⁸

Age at First Full-term Pregnancy

In general, parous women have a lower risk of breast cancer than nulliparous women. A majority of the studies report a lower risk of developing breast cancers with a first full-term pregnancy at a younger age.⁷ This trend may be related to the maturation of glandular epithelium of the mammary cells, which occurs in the first pregnancy.⁹

Number and Spacing of Births

Each additional childbirth beyond the first generally reduces the long-term risk of developing breast cancer. This beneficial effect is more pronounced with more closely spaced births.¹⁰

Lactation

As early as 1926 it was observed that women who never lactated were more prone to develop breast malignancy.¹¹ The balance of evidence from case control and cohort studies support the reduction in the risk with a longer duration of breast-feeding. However, the estimated level of risk reduction has varied substantially. The most favorable results indicate at least a 50% reduction in the risk for women who breast feed each child for two or more years.¹²

Age at Menopause

Bilateral oophorectomy before the age of 45 reduces the risk of breast cancer by 50% as compared to women who have natural menopause at age 55 years or later.¹³ It has been estimated that the risk of breast cancer increases by approximately 3% per year for menopause beyond the age of 45. This delay in menopause causes a longer exposure to endoge-

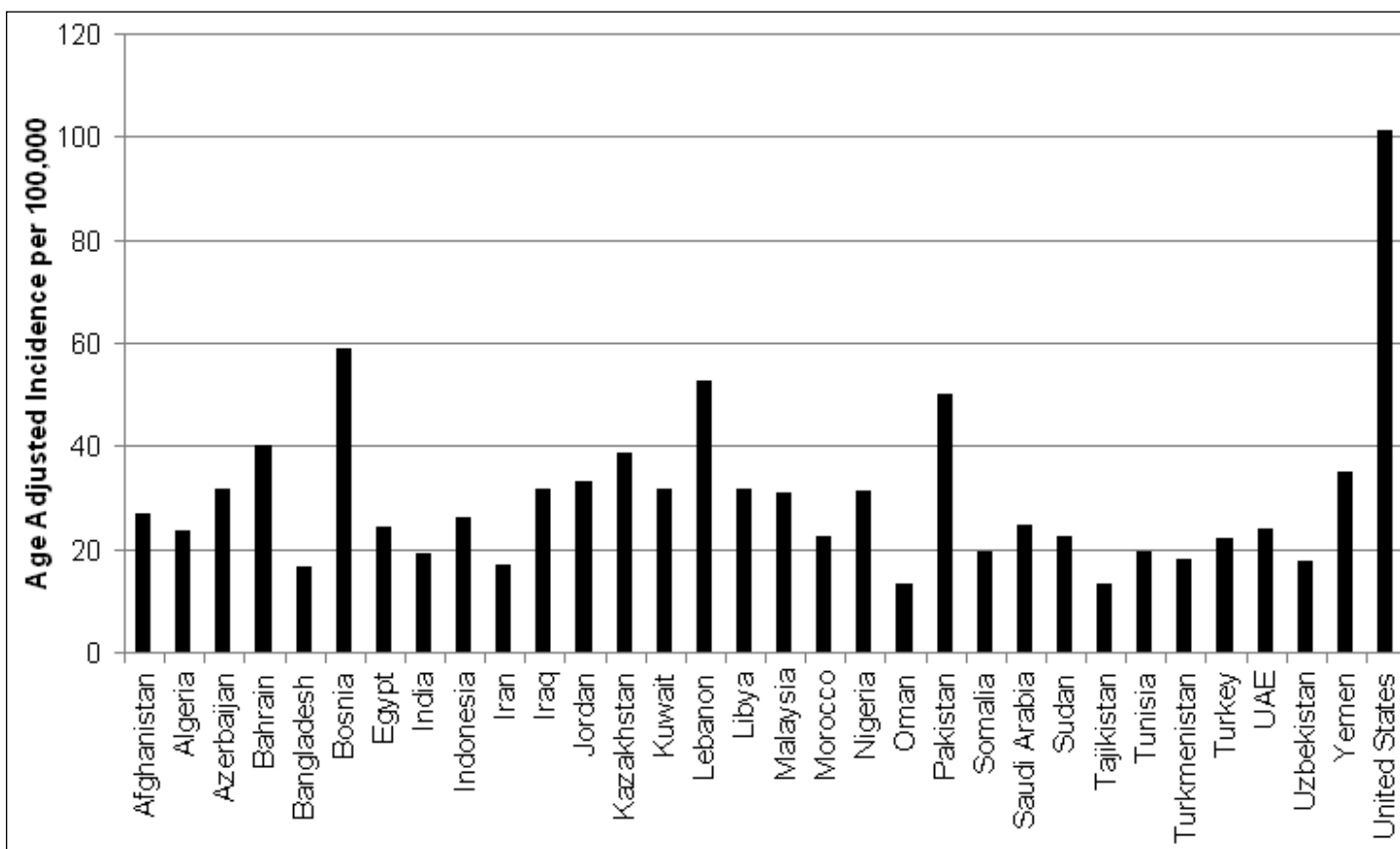


Figure 1. The incidence of breast cancer through 2000 in various Muslim countries, as derived from the WHO's GLOBOCAN 2002 database.⁴

nous hormones and continued proliferation of the ductal epithelium.

Oral Contraceptives

Multiple studies suggest that the use of oral contraceptives does not increase the risk for breast cancer.¹⁴ However, the use of oral contraceptives before the first full-term pregnancy or before the age of 20 may result in a modest increase in risk.¹⁵

Postmenopausal Hormone Replacement

The Women's Health Initiative, a large randomized study of more than 16,000 women in the U.S., revealed that combined estrogen and progestin replacement in postmenopausal women increased the risk of breast cancer by 26%.¹⁶

2. Family history and genetic syndromes

Five to ten percent of the breast cancers in the Western world are directly related to genetic mutations.¹⁷ The two most frequent are autosomal dominant mutations of BRCA1 and BRCA2. The risk of these patients developing breast cancer is estimated

to be 36% to 87%.¹⁸ The incidence of BRCA1 and BRCA2 among women in Muslim countries has been reported to be similar to that of Western women in at least one study from Pakistan and another from Turkey.^{5,19}

A family history of breast cancer significantly increases the risk in a given individual. The relative risk of developing cancer is

- (a) 1.5 times greater if a first-degree relative developed breast cancer postmenopausally, and
- (b) 2.0 times greater if a first-degree relative developed breast cancer premenopausally.

If two or more first-degree relatives had breast cancer, the risk is increased almost six-fold. Additionally, a first-degree family member having had bilateral breast cancers also raises the risk six-fold.²⁰

3. Dietary factors

Nutritional factors have been extensively evaluated to account for the varying incidence of breast cancer across the world. The nutritional hypothesis

Table 1. Relative risks, including age, previous breast disease, mammographic density, and radiation exposure.

Risk Factors	Risk Categories	Relative Risk
Age ²⁶	>65 years vs. <65 years	5.8
Age at menarche ⁷	<12 years vs. >15 years	1.3
Age at menopause ¹³	>55 years vs. <45 years	2.0
Age at first live birth ⁷	>30 years or nulliparity vs. <18 years	1.9
Combined postmenopausal hormone replacement therapy ¹⁶	Current use or at least 5 years of use vs. no use	1.6
Previous breast disease ²⁶	Hyperplasia without atypia vs. no breast biopsy	1.5-2.0
	Atypical ductal hyperplasia vs. no breast biopsy	4.0-5.0
	Atypical lobular hyperplasia vs. no breast biopsy	4.0-5.0
	Lobular carcinoma in situ vs. no breast biopsy	8.0-10.0
	Ductal carcinoma in situ vs. breast biopsy	4.0-10.0
Mammographic density ²⁶	Dense breast tissue vs. little or no density	4.0-6.0
Obesity (postmenopausal) ²¹⁻²	Body mass index ≥ 25 kg/m ² vs. body mass index <25 kg/m ²	1.3-2.1
Physical activity ^{29,32}	Inactivity vs. regular activity	1.25-1.4
Alcohol use ²³	>3 drinks per day vs. no drinks	1.46

has also been used to explain the increase in the risk of migrant populations. However, it has been difficult to prove a direct correlation between diet and breast cancer. The association may be more complex and probably related to weight. Weight gain after age 18 is associated with a greater risk for developing postmenopausal breast cancer.²¹⁻² Following the diagnosis of breast cancer, either weight loss or weight maintenance decreases the risk of relapse.²³

Scientific data has consistently shown that even a modest intake of alcohol in women increases the risk of breast cancer.^{22,24}

4. Physical activity

Prospective and retrospective studies clearly demonstrate a reduced risk of breast cancer with regular physical activity.²⁵ This can perhaps be explained by the link between physical activity and weight. Vigorous physical activity in girls before the onset of menarche also reduces the risk of breast

cancer by delaying the onset of ovulatory cycles, which decreases lifetime exposure to estrogens.²⁶ Physical activity also seems to decrease the risk of relapse once breast cancer is diagnosed.²²

Table 1 summarizes the risk factors' relative risks, including age, previous breast disease, mammographic density, and radiation exposure.²⁷

Risk Assessment

Risk reduction of breast cancer requires first estimating the individual's risk, then applying strategies to reduce this risk. Estimating the risk for a given patient requires a complete evaluation with special attention to all known risk factors. Two models are commonly used clinically to estimate an individual's risk. The Gail model, based on data from U.S. cancer registries, is widely used. It combines 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.²⁸ The model incorporates a variety of risk factors to assess a patient's risk as compared to the average American. A 5-year cumulative risk of at least 1.67 times greater than a normal is defined as high risk. The model has not been validated in non U.S. populations. The Gail model does not place a significant emphasis on family history. The Claus model is more suited for women with a family history of breast cancer.²⁹

Biology of Breast Cancer

The current model of the development of breast cancer hypothesizes that a normal cell undergoes hyperplasia, which evolves into atypical hyperplasia, further progressing to in situ cancer, and finally invasive cancer. The cancer becomes radiographically detectable at 1 mm and clinically palpable at 1 cm. This transformation from a normal cell to the earliest clinically detectable cancer occurs over several years.³⁰ This duration provides many opportunities to stop the progression and prevent the development of invasive disease (Figure 2).

Strategies for Risk Reduction

The pathophysiology and the gradual evolution of breast cancer make it suitable for intervention at various stages. General risk reduction strategies, applicable to all women, include balanced diet, physical activity, weight management, and breast-feeding. These simple measures could reduce the risk by as much as 40%. Primary care physicians should be reminded to ask their patients about family history of cancer. Those with family history of breast cancer should be referred for genetic counseling for risk stratification. Testing for BRCA1 and BRCA2 can be offered. These women should be encouraged to modify their lifestyle risks, perform self-breast examinations and seek regular clinical follow-up. Regular screening with mammography could detect cancers early, leading to better long-term outcomes. Medical interventions can forestall the development of clinical disease and prevent morbidity and mortality in high-risk women.

Physical Activity

There is convincing evidence that the risk of breast cancer can be reduced by increasing physical activity. There are several studies that have shown a consistent pattern of risk reduction, including

prospective studies.^{22-3,31-2}

Diet

The role of diet as a means of reducing the risk of breast cancer remains unsubstantiated. Results of prospective studies do not support a significant role of dietary fat being the cause of breast cancer. However, weight gain in the middle age years is associated with an increased risk. Available evidence suggests that minimizing weight gain in adulthood is associated with a decrease in the risk.²²⁻³

Alcohol consumption is forbidden in Islam. However, it is available in Muslim countries. Avoiding alcohol reduces the risk.^{22,24}

Breast Self Examination

Randomized trials have not demonstrated a survival benefit for breast self examination (BSE). However, BSE is noninvasive, does not cost anything to the patient, and 75-90% of invasive breast cancers are discovered by the patient. BSE has been correlated with a more favorable clinical stage. It can be a valuable tool in countries with limited medical resources lacking more sophisticated screening methodologies.³³⁻⁴

Clinical Breast Exam

Mammographic screening without a clinical breast exam (CBE) is incomplete, as about 15% of cancers missed by mammography are detected by CBE. 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.³³

Mammography

Mammography in randomized trials was shown to reduce mortality by 30% with annual or biennial screening in women aged 50 to 69 years. Data from women younger than 50 is less clear, probably from shortcomings of study design and the small number of women screened.³⁵

Bilateral total mastectomy

Two small prospective studies with a relatively short follow up show that women with BRCA1 and BRCA2 can achieve a high degree of protection by having a bilateral total mastectomy.³⁶⁻⁷ Retrospective follow up of 13 to 14 years in women with BRCA1 and

BRCA2 who underwent bilateral mastectomy reveals a 90% risk reduction.³⁸⁻⁹

Bilateral salpingo-oophorectomy

Bilateral salpingo-oophorectomy at or before the age of 40 in women with BRCA1 and BRCA2 mutations reduces the risk of breast cancer by approximately 40%.⁴⁰ These women are also at an increased risk of ovarian cancer, although it is a much lower risk than breast cancer. A salpingo-oophorectomy would accomplish the dual purpose of reducing the risk of both ovarian and breast cancer.

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. They were utilized in women 35 or older, with a predicted Gail model risk of greater than 1.67.⁴¹⁻² An overview of four studies reveals a 38% reduction in the risk of developing breast cancer.⁴³

It is currently recommended that women at high risk, over the age of 35 with a Gail model rating of 1.7 or greater, consider taking 20 mg of oral Tamoxifen for 5 years.

Raloxifene, a second generation SERM, is as effective as Tamoxifen in reducing risk, as shown in a randomized trial of almost 20,000 women. Raloxifene, however, may be the preferred drug because of its lower incidence of side effects.⁴⁴

Table 2 summarizes general measures of breast cancer prevention. Table 3 identifies appropriate medical management based on risk status.⁴⁵⁻⁶

Social Consequences of Breast Cancer in Muslim Countries

Of the women who present with early stage breast cancer, 75% are from higher socioeconomic groups and generally more educated. Approximately 90% of these women receive adequate treatment resulting in overall survival of about 75% at 10 years. In contrast, about 50% of the women who present with advanced disease are from a poor socioeconomic and low educational background. Of these economically challenged women, only 44% receive adequate treatment resulting in a 10-year survival of 50%.³ Literacy and ignorance play a major role in determining the prognosis. The stigma attached to

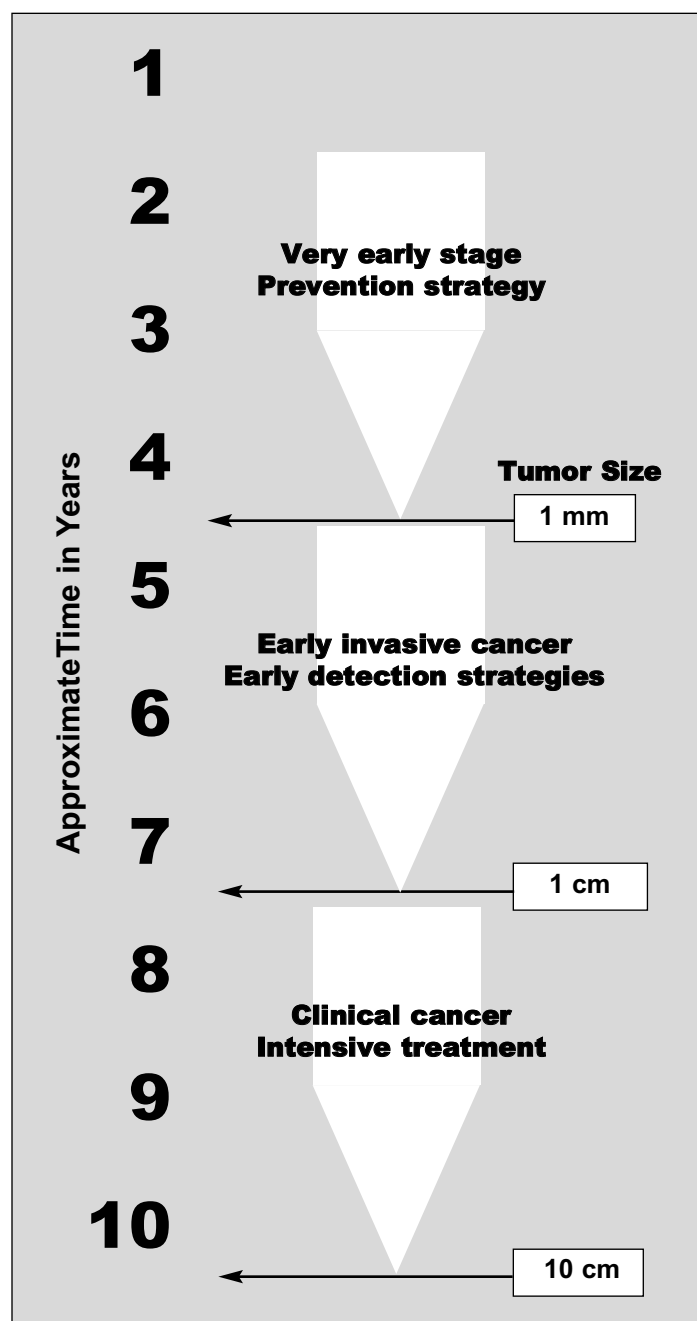


Figure 2. Biological evolution of breast cancer.

breast cancer in Muslim countries, especially in the lower socioeconomic group and in poorly educated women, presents a significant barrier. This barrier creates a reluctance to seek medical aid, as well as having the woman exhaust alternative treatment options before seeking appropriate medical help, thus delaying the diagnosis and allowing the cancer to become more advanced.

Islamic Perspective on Preventive Health

Long before Western medicine discovered the

Table 2. Prevention Strategies: General Measures.

Type of Intervention	Possible Mechanism of Action	Possible Ways to Achieve Them	Relative Risk Reduction
Physical activity ^{29,32}	Lowers body fat, enhances immune function, affects hormone levels and delays menarche	Individual: exercise/education, planned/mandatory exercise programs	20-30%
Healthy dietary habits ³¹		Community education: legislation requiring food labeling, controlling school lunch menu	
Postmenopausal weight management ^{21,22}	Adipose tissue stores hormones	Community education improving access to physical fitness facilities	20-30%
Avoidance of hormone supplements ¹⁶		Physician education	26%
Breast feeding ^{11,12}	Maturation of ductal epithelium	Education/providing facilities at work environment	4% reduction for every 12 months of breast feeding
Childbearing patterns (first live birth under 18 vs. over 30 or nulliparity) ^{7,10}	Early pregnancy causes terminal differentiation of ductal epithelium	Education	40%

value of preventative medicine, Islam recognized its importance. In the Qur'an, Allah ﷻ says:

وَكُلُوا وَاشْرَبُوا وَلَا تُسْرِفُوا

[E]at and drink, but avoid excess.⁴⁷

Following this principle prevents obesity, minimizing the risk of breast cancer among many other illnesses.

The Qur'an also contains another example of preventative medicine that further reduces the risk of developing breast cancer specifically. Allah ﷻ specifically states that complete breastfeeding lasts for 2 years:

وَالْوَالِدَاتُ يُرْضِعْنَ أَوْلَادَهُنَّ حَوْلَيْنِ كَامِلَيْنِ لِمَنْ أَرَادَ أَنْ يُتِمَّ الرَّضَاعَةَ

Mothers shall suckle their children for two whole years; (that is) for those who wish to complete the suckling.⁴⁸

The wisdom of this verse is confirmed by modern scientific observations.¹²

Conclusion

The incidence of breast cancer in Muslim countries is on the rise. The nature of breast cancer, with its many modifiable risk factors and prolonged time of evolution, make it an ideal disease for preventive interventions. The risk of acquiring breast cancer can be reduced by simple modifications in diet, lifestyle, and health screening. An intensive campaign to shift the focus of the *umma* (the worldwide Muslim community) from treatment to risk reduction strategies and early detection can help decrease the incidence and mortality of breast cancer substantially. Every effort must be made to remove the stigma associated with this disease, to allow every

Table 3. Appropriate medical management based on risk status.

	Risk Status	Management
Average risk ⁴⁷	5 years Gail model risk < 1.67%	<ul style="list-style-type: none"> • Annual physical examination • Annual screening mammogram (beginning at age 40 years) • Encourage breast self-examination • Reassess risk every 2-3 years
High risk ⁴⁸	5 years Gail model risk > 1.67%	<ul style="list-style-type: none"> • Physical examination every 6-12 months • Annual mammogram (beginning at age 40 years) • Encourage breast self-examination • Consider tamoxifen or raloxifene
High risk ⁴⁸	Prior thoracic radiation therapy	<ul style="list-style-type: none"> • Physical examination every 6-12 months • Annual mammogram (beginning 8-10 years after radiation therapy or at age 40, whichever is first) • Encourage breast self-examination • Consider tamoxifen (Role of tamoxifen unclear in women with history of thoracic irradiation and those with known BRCA1 and BRCA2 mutations.)
High risk ⁴⁸	Atypical lobular or ductal hyperplasia	<ul style="list-style-type: none"> • Physical examination every 6-12 months • Annual mammogram • Encourage breast self-examination • Consider tamoxifen or raloxifene (Greatest risk reduction seen in women with atypical hyperplasia.)
	Strong family history or known genetic predisposition	<ul style="list-style-type: none"> • Physical examination every 6-12 months • Annual mammogram (beginning at age 25 or 5-10 years before earliest index case) • Encourage breast self-examination • Consider tamoxifen (Role of tamoxifen unclear in women with history of thoracic irradiation and those with known BRCA1 and BRCA2 mutations.) • Consider prophylactic mastectomy • Consider prophylactic oophorectomy

Muslim woman the best chance for survival. This will require a joint effort by physicians and religious institutions.

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