



Science

QATAR'S EXPERIENCE WITH HEREDITARY BREAST AND OVARIAN CANCER AND HIGH RISK CLINIC: A RETROSPECTIVE STUDY 2013- 2016

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Abstract

Introduction: Approximately 5%-10% of breast cancer is hereditary and BRCA1 and BRCA2 genes are responsible for most of the cases. In the State of Qatar, the cancer genetics program was established at National Center of Cancer Care and Research on 2013 which is considered the first of its kind in the region dedicated exclusively to providing genetic counseling, risk assessment and management of high risk patients and their families. In this study, we aim to describe our experience with the hereditary cancer and high risk clinic from the period of March 2013 until December 2016. **Methods:** In this retrospective study, a total of 697 patients were evaluated at the high risk clinic between March 2013 to December 2016. High risk patients were either placed under surveillance or offered genetic testing for the BRCA genes. **Results:** A total of 697 patients were evaluated at the high risk clinic in which 347 patients were considered eligible for high risk screening. 167 patients pursued genetic testing and 64 patients (38%) had BRCA mutations with BRCA1 being the most common, while 72 patients (43%) were BRCA negative. A total of 31 patients (19%) had variants of unknown significance in the BRCA genes. Most of the BRCA positive patients 63% were affected with either breast and/or ovarian cancers and were within younger age group, while 38% were unaffected. 55% of those BRCA positive affected patients had triple negative breast cancer. The prevalence of BRCA mutations among Qatari breast cancer patients reaches up to 10% while it reaches approximately 3.5% among non-Qatari breast cancer patients. **Conclusion:** Our program is an example of a well-established and multidisciplinary service targeted toward prevention and personalized medicine in high risk patients that goes in line with Qatar's 2022 vision of achieving excellence in cancer care. From our unique experience, we show that BRCA mutations are prevalent among Qatari breast cancer patients reaching approximately 10% which can partially explain the young onset diagnosis of breast cancer in Qatar. With the higher awareness about our service and the recent establishment of BRCA testing at HMC, it is believed that the prevalence of BRCA is going to increase. In addition, with the introduction of multigene panel at our clinic, we believe that it will provide us

with new perspective on all hereditary cancers. Our data registry on hereditary cancer syndromes will open windows for future research on cancer prevention and targeted therapies.

Keywords: Breast Cancer; Genetic Counseling; BRCA Genes; HBOC; Surveillance; Prophylactic Surgery.

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1. Introduction

Breast cancer is the most common malignancy and the second leading cause of cancer death among women [1]. Most women with breast cancer have a sporadic rather than an inherited breast cancer, however, 5-10% of breast cancer cases has been attributed to hereditary components [1]. Early onset at diagnosis and family history of breast and ovarian cancers are generally considered indicators of genetic susceptibility to breast and ovarian cancers [2]. In addition, breast and ovarian cancer histopathological features are important indicators for hereditary breast and ovarian cancers. For example, in a recent study, we showed that breast cancers associated with breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2) mutations are likely to be basal sub-type and exhibits more aggressive behavior, particularly in younger age groups and those patients present with a more advanced stage of disease than those with no pathogenic mutations in the BRCA genes who exhibit a less aggressive disease [3].

Hereditary breast and ovarian cancer syndrome is the most common cause of hereditary forms of both breast and ovarian cancers that results due to mutations in the BRCA1 and BRCA2 genes [2]. The prevalence of BRCA1/2 mutations is estimated to be 1 in 400 to 1 in 800 in the general population and approximately 3% among women with breast cancer but varies considerably and is significantly higher in certain ethnic groups due to founder effects [4, 5]. For example, individuals of Ashkenazi (central European) Jewish ancestry have an increased prevalence of BRCA mutations with a carrier frequency of approximately 1 in 40 and approximately a prevalence of 10% among women with breast cancer due to the presence of three founder mutations in the BRCA genes [4,5]. In individuals who carry mutations within the BRCA1 or BRCA2 genes, the risk of developing breast and ovarian cancers is thought to be approximately 45% to 87% for breast cancer by age of 70 and approximately 45% to 60% for ovarian cancer among BRCA1 mutation carriers and 11% to 35% among BRCA2 mutation carriers [6]. In BRCA1/2 carriers, the risk for contralateral breast cancer is also increased which can reach up to 27% within 5 years of the initial breast cancer diagnosis in BRCA1 carriers and 12% for BRCA2 carriers [7]. In addition to breast and ovarian cancers, BRCA1/2 mutation carriers have an increased risk for male breast and prostate cancers with a life time risk reaching up to 5-10% for breast cancer and up to 15% for prostate cancer especially among BRCA2 mutation carriers [7,8,9].

The State of Qatar is a peninsula in the east of Arabia, bordering the Persian Gulf and Saudi Arabia, with a heterogeneous population of approximately 2 million people (Donnelly, et al 2013). Individuals of non-Qatari ethnicity account for most of the population accounting for 86%, in comparison to individuals of Qatari ethnicity who account for only 14% of the population [9]. In the State of Qatar, breast cancer is the most common cancer among women with prevalent age group of 45 years old accounting for 36% of all affected women [10]. The incidence rate increased from 45 per 100,000 in 2003-2007 to 56 per 100,000 in 2008-2011 [10]. Patients of Qatari ethnicity account for 32% of all the diagnosed breast cancers in females [10].

In the State of Qatar, the cancer genetics program and hereditary breast and ovarian cancer and high-risk clinic was established on 2013 at the National Center of Cancer Care and Research (NCCCR) dedicated exclusively to providing genetic counseling, risk assessment and management for patients and their families at high risk for different malignancies. In this retrospective study, we aim to describe our experience with the hereditary breast and ovarian cancer high risk clinic from the period of March 2013 until December 2016 through which we aim to explore the characteristics of BRCA carriers and to explore the prevalence of BRCA mutations among the breast cancer patients in the State of Qatar and especially among those of Qatari ethnicity.

2. Materials and Methods

The cancer genetics program and the hereditary cancer and high-risk clinic was established officially on March, 2013 at the National Center of Cancer Care and Research (NCCCR) by Dr. Salha Bujassoum Al-Bader, a senior medical oncologist and the director of the cancer genetics program. The aim behind establishing this program and clinic was to manage all affected and unaffected high risk patients and their families who are at increased risk for developing cancers due to carrying a hereditary predisposition or due to past exposure or other risk factors and offering them risk reducing strategies. Through our service, we also contribute in guiding the patient's treatment management, through genetic testing that can help to offer some patient's targeted therapies which improve patient's treatment significantly. From 2013 until 2015, the clinic was mainly managing patients with hereditary breast and ovarian cancers, however, in 2016; the clinic has been expanded to manage patients at high risk for gastrointestinal and other hereditary cancer syndromes. This service is considered the first of its kind in the region that is supported by board certified medical oncologists and board certified genetic counselors. Patients are often referred to the high risk clinic from different departments at Hamad Medical Corporation (the main governmental hospital), primary health centers, and private hospitals and even from other neighboring countries. Patients are often referred due to personal history of young onset cancers such as breast, ovarian and colon cancers or due to extensive family history of different malignancies or due to past exposure or other risk factors. At the hereditary and high risk clinic, patients are assessed through different evaluation clinic visits with the medical oncologist and the genetic counselor where patients are stratified into low risk or high risk. The medical services are delivered to patients through a multidisciplinary team where focal points were assigned in different specialties to serve this high risk population including breast surgery, plastic surgery, gynecology, and gastroenterology as well as other specialties.

The pathway of the hereditary and high risk clinic is illustrated in the clinic pathway as shown in Figure 1. High risk patients are either placed under high risk surveillance or are offered genetic testing based on personal and family histories, risk assessment models and following international guidelines such as National Comprehensive Cancer Network (NCCN) and the National Institute for Clinical Excellence (NICE). Through shared decisions and multidisciplinary approach, patients are offered several risks reducing strategies including prophylactic surgery, surveillance or chemo-prevention based on our established guidelines for managing patients with different hereditary cancer syndromes and supported by well-known established international guidelines. The high risk clinic also helps to stratify the risk of the patient’s family members through offering them genetic counseling, predictive testing and risk reducing strategies.

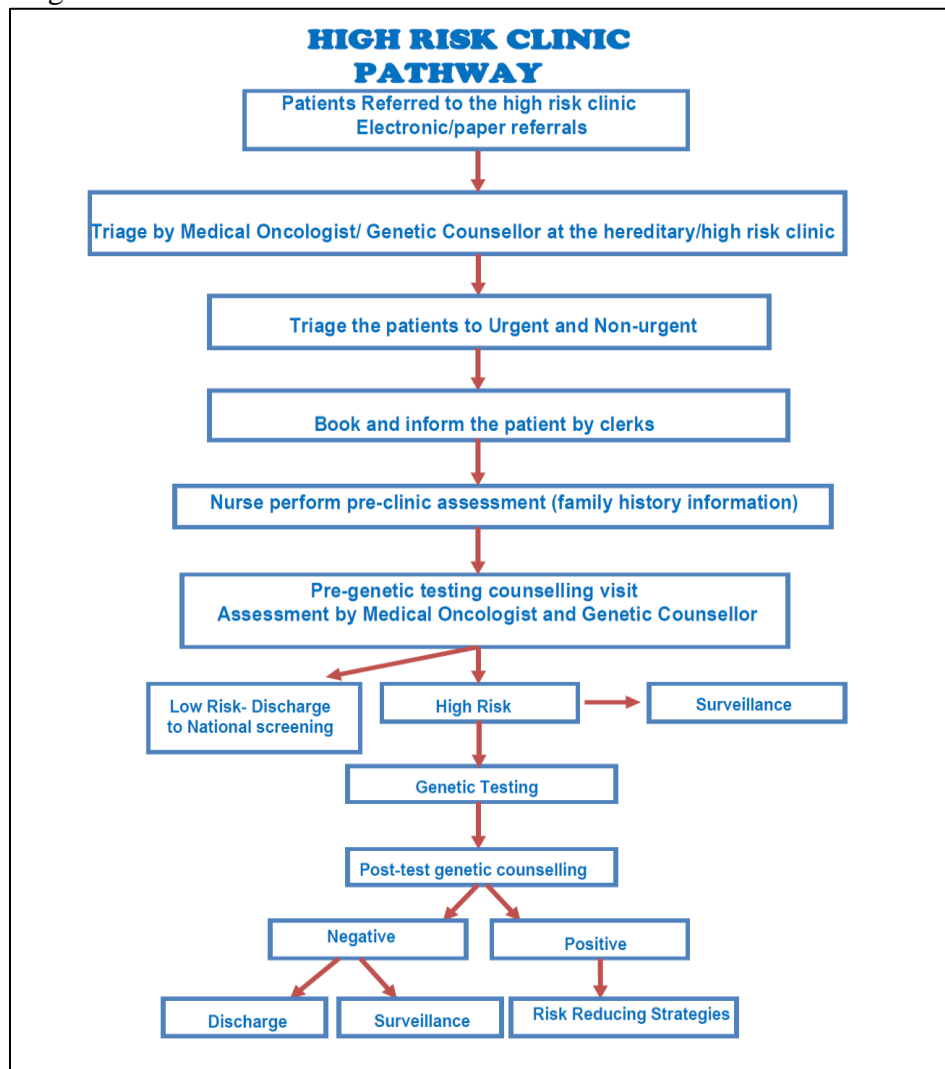


Figure 1: Pathway of the hereditary/high risk clinic

In this retrospective study, the data from our hereditary cancer registry was evaluated for the period between March 2013 to December 2016. A total of 697 patients were evaluated at the high risk clinic between 2013 to 2016 where patients were stratified based on their risk. High risk patients for hereditary breast and ovarian cancer syndrome were offered genetic testing for

the BRCA1 and BRCA2 genes. Patients were offered testing for BRCA-1/2 full sequencing and multiple ligation dependent probe amplification (MLPA) at a CAP accredited lab. Blood was collected in EDTA tubes and was sent for molecular testing. DNA was extracted using standard methods. Samples were analysed using direct DNA sequencing of all coding regions and intron-exon junctions and was evaluated for any deletions or duplications through both sequencing analysis and MLPA.

This study was conducted in the State of Qatar at the National Centre of Cancer Care and Research; ethical approval was granted by the research ethics committee of the Hamad Medical Corporation (HMC RP #14126/14) on March 26th, 2014.

2.1. Statistical Analysis

Statistical analyses were performed using the statistical package STATA statistical software package version 12.0 to exploratory data analysis and descriptive statistics.

Descriptive analysis was performed to characterize the demographic variables of the patients. Mean and standard deviation (SD) were described for the continuous variables with normal distribution and ranges for the continuous variables with skewed distribution. Frequencies and proportions were used for categorical variables.

The frequency distribution of the variables studied is presented with their respective 95% confidence intervals.

3. Results and Discussions

A total of 697 affected and un-affected individuals were referred to the hereditary and high risk clinic from the period of March 2013 until December 2016 due to either personal or family history of breast and/or ovarian cancers. A total of 347 patients were considered eligible for high risk screening. Out of the 347 high risk patients, a total of 180 patients were eligible for breast/ovarian cancer increased surveillance and 167 patients elected genetic testing after formal assessment by a board certified genetic counselor. Out of the 167 patients who pursued genetic testing, a total of 64 patients (38%) had BRCA mutations, while 72 patients (43%) were BRCA negative. A total of 31 patients (19%) had variants of unknown significance in the BRCA genes (Figure 2).

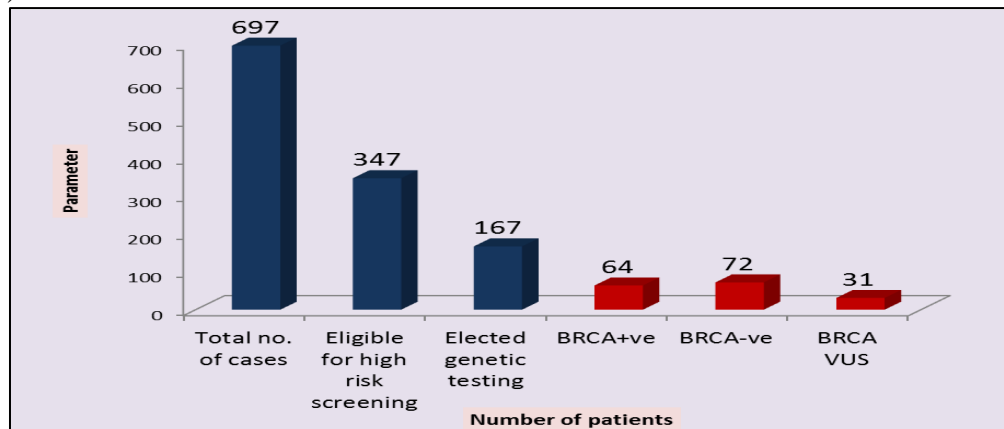


Figure 2: High Risk Clinic data (March 2013-December 2016)

3.1. Characteristics of BRCA Carriers

Most of the BRCA positive patients, 63% were affected with either breast and/or ovarian cancers and were within the younger age group (36-40 years of age) while 38% of patients were unaffected and were younger than 41 years of age. A total of 60 patients were females, while four patients were males. Most of the BRCA positive patients were of Qatari ethnicity followed by those of other Arabic and other ethnicities (Table 1). This is most likely due to the fact that BRCA genetic testing was often sent abroad when the clinic was first opened and it was costly for non-Qatari patients to pay for genetic testing.

Table1: Demographics of BRCA positive patients

	Affected	Un-Affected
Parameter		
Age-group		
Less than 25	0%	17%
26-30	13%	17%
31-35	15%	13%
36-40	28%	17%
41-45	18%	4%
46-50	8%	13%
51-55	5%	13%
56-60	5%	8%
61-65	8%	0%
65+	0%	0%
Nationality		
Qatari	41%	79%
Arabic	33%	8%
Others	26%	13%

Among affected BRCA positive patients, a total of 41 patients had breast cancer, while one patient had ovarian cancer. The most common indication for genetic testing among affected BRCA positive patients was having triple negative breast cancer (defined by the absence of three markers: estrogen and progesterone receptors, and human epidermal growth factor (HER)-2 expression) either with or without family history (55%) followed by those with breast cancer (of other histopathological features) older than the age of 40 but with positive family history of breast and ovarian cancers (16%) followed by those with breast cancer diagnosed (other than triple negative) before the age of 40 with or without family history (13%) (Figure 3). In our BRCA positive patient cohort, all BRCA positive affected patients who were diagnosed older than the age of 40 had family history of breast and ovarian cancer unlike those who were diagnosed younger than the age of 40 in which most of them had no family history and their young age at diagnosis was the only indication for genetic testing (Figure 3). In regards to the unaffected BRCA positive patients, 83% of them were offered genetic testing due to the presence of familial mutation in a blood relative (Figure4).

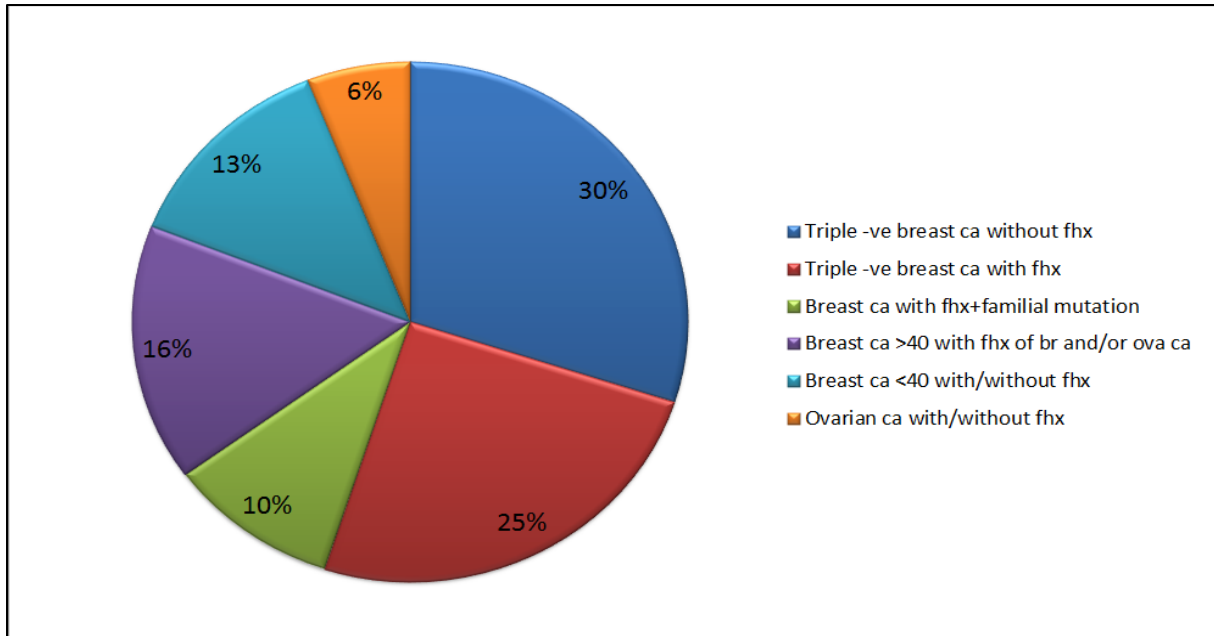


Figure 3: Genetic testing indications among affected BRCA carriers

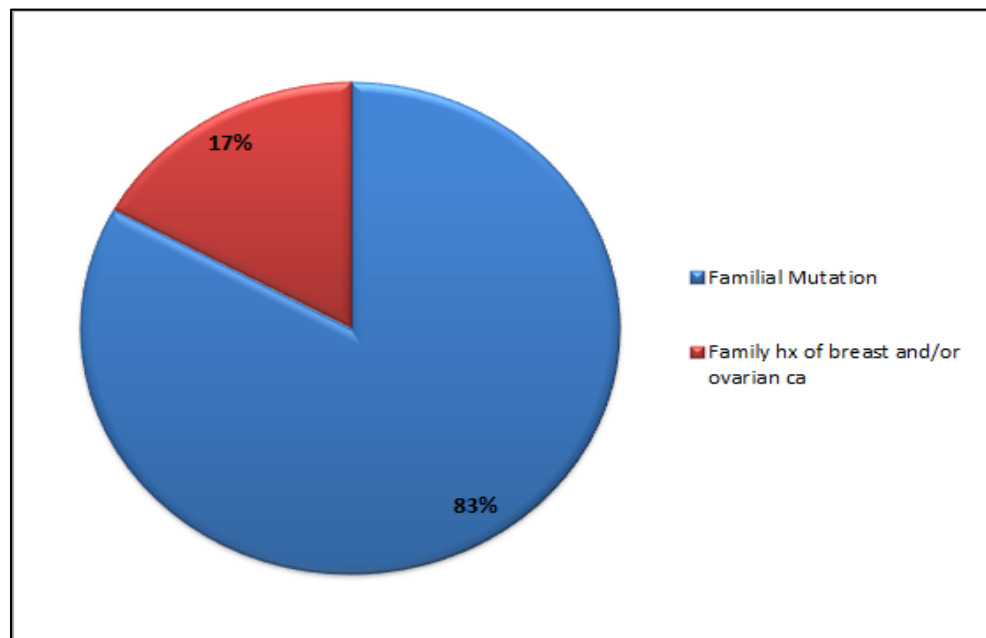


Figure 4: Genetic testing indications among un-affected BRCA carriers

Most of the BRCA positive patients were BRCA1 positive (N=50) followed by BRCA2 (N=12) with most mutations being frameshit. Two patients were found to have mutations in both BRCA1 and BRCA2 genes (Figure5). A total of 28 patients with BRCA1 mutations were affected, while 22 patients were unaffected. On the other hand, a total of 10 patients with BRCA2 mutations were affected, while 2 patients were unaffected. Both of the two patients who carried mutations in both of BRCA1 and BRCA2 mutations were affected (Table 2).

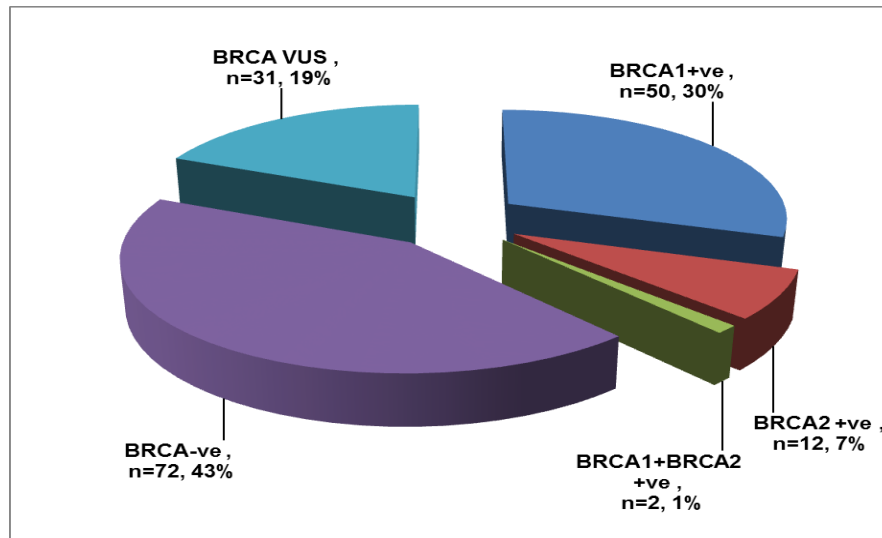


Figure 5: Distribution of BRCA mutations among high risk patients

Table 2: Distribution of BRCA mutations among affected and unaffected patients

BRCA+ve	Affected	Unaffected
BRCA1+ve	28	22
BRCA2+ve	10	2
BRCA1+BRCA2 +ve	2	0

3.2. Prevalence of BRCA Mutations among Breast Cancer Patients (Qatari Versus Other Ethnicities)

The prevalence of BRCA mutations among women with breast cancer in the State of Qatar was calculated in those who are of Qatari ethnicity versus those of non-Qatari ethnicity (including Arabs of the Middle East and other non-Arabs patients). The prevalence of BRCA mutations in breast cancer was calculated through getting the data on breast cancer diagnoses and the number of BRCA carrier from the period of January 2013 until December 2016 for Qatari and non-Qatari breast cancer patients as shown in Table 3. The prevalence of BRCA mutations in Qatari breast cancer patients was found to be 10%, while it was found to be 3.5% in those of non-Qatari ethnicity.

Table 3: The prevalence of BRCA mutations in Qatari versus non-Qatari breast cancer
Numbers of breast cancers diagnoses and prevalence of BRCA mutations
(January 2013- December 2016)

	Number of breast cancer diagnoses (2013-2016)	Number of affected BRCA mutation carriers (2013-2016)	Prevalence of BRCA mutations in affected women, %
Qatari	188	19	10 %
Non-Qatari	737	26	3.5%
All	925	45	13.5 %

4. Discussion

Although most cases of breast and ovarian cancers are thought to be sporadic, approximately 5-10% of breast and ovarian cancer cases have been attributed to hereditary components. Hereditary breast and ovarian cancer syndrome account for most of the cases of hereditary breast and ovarian cancers and is caused by mutations in the BRCA1 and BRCA2 genes. In the State of Qatar, the cancer genetics program and the hereditary cancer and high risk clinic was established on 2013 which is considered the first of its kind in the Middle East which aims to serve all affected and unaffected high risk patients and their families who are at increased risk for developing cancers due to hereditary and non-hereditary causes and offering them risk reducing strategies through shared decision and multidisciplinary approach. In this study, we describe our experience with the hereditary breast and ovarian cancers from the period of March 2013-December 2016.

A total of 697 patients were evaluated at the high risk clinic between March 2013 to December 2016. A total of 347 patients were considered eligible for high risk screening in which 180 patients were eligible for breast/ovarian increased surveillance and 167 patients elected genetic testing after formal assessment by a board certified genetic counselor. Those patients who were assessed to be at high risk for hereditary breast and ovarian cancer syndrome were offered genetic testing for the BRCA1 and BRCA2 genes. Out of the 167 patients who pursued genetic testing, 38% had BRCA mutations, while 43% were BRCA negative and 19% had variants of unknown significance in the BRCA genes. These results weren't surprising as BRCA mutations accounts for only 5-10% of breast and ovarian cancers [1] and it's believed that the BRCA negative high risk patients in this study might have had mutations in other genes associated with breast and ovarian cancers that would have been detected if they were offered multi-gene testing. In our patient's cohort, most of the BRCA positive patients had young onset breast cancer in which most of them were diagnosed between the ages of 36-40 years of age and were of Qatari ethnicity. This comes in line with the previous literatures in which the breast cancer diagnoses associated with hereditary breast and ovarian cancer syndrome is often young onset [1, 3, 7]. In this study, most of the BRCA positive affected patients were of Qatari ethnicity. This is most likely due to the lower uptake of genetic testing among non-Qatari patients because of the high cost of genetic testing and the difficulty in tracing non-Qatari's affected family members who live outside Qatar.

In our study, we showed that most of the BRCA positive patients were affected with triple negative breast cancer and had deleterious mutations within the BRCA1 gene. In addition, we found that the most common mutations observed in the BRCA positive patients were frame shift mutations resulting in non-functional proteins. This comes in line with the previous studies [11,12] including our recent publication [3] which showed the significant association between BRCA1 mutations and triple negative breast cancer and that frame shift mutations are the most common type of mutations occurring in the BRCA genes [3, 11, 12].

In our study, we found that all BRCA positive affected patients who were diagnosed above the age of 40 have had positive family history of breast and ovarian cancers unlike those who were diagnosed younger than the age of 40 in which most of them had no family history of cancers and that their young age at diagnosis was the only indication for genetic testing. This had lead us

to adjust our testing criteria for the BRCA genes for those diagnosed with breast cancer and the age cutoff was reduced from ≤ 45 to ≤ 40 for those diagnosed with breast cancer (except triple) and who report no family history of cancers based on our experience and patient population. The other testing indications have stayed the same following the NCCN and NICE guidelines.

In terms of the BRCA positive unaffected patients, we showed that most of the unaffected BRCA positive patients (83%) have been offered genetic testing due to the presence of a known familial mutation in a blood relative. This result shows that most of the un-affected at risk patients were motivated to pursue predictive genetic testing which is most likely due to the nature of the clinic that ensures the safety and confidentiality of patients and their family members through pursuing a culturally sensitive approach when counseling and disclosing results to those families.

Finally, in our study, we were able to calculate the prevalence of BRCA mutations in breast cancer patients in the State of Qatar and with a great focus on those of Qatari ethnicity. According to the previous literature reviews, the prevalence of BRCA mutations among women with breast cancer in general population is estimated to be 1-3% and is higher among those younger than the age of 40 which can reach up to 6% [13]. In this study, we found out that the prevalence of BRCA mutations among Qatari breast cancer patients reaches up to 10% which is higher than the reported prevalence of BRCA mutations among breast cancer patients in the general population [13]. However, our reported prevalence of BRCA mutations among those of Qatari ethnicity is similar to the prevalence of BRCA mutations among breast cancer patients of Ashkenazi Jewish ancestry who are diagnosed at any age in which the carrier rate is estimated to be 10% [14]. It is however known that the prevalence of BRCA mutations is significantly higher among Ashkenazi Jewish breast cancer patients who are diagnosed younger the age of 40 which can reach up to 35% [14]. This high prevalence of BRCA mutations among the Qatari breast cancer patients can partially explain the young onset diagnosis of breast cancer in the State of Qatar but this warrants further research in the future.

Due to the high rate of consanguinity in the State of Qatar especially among those of Qatari ethnicity which reaches up to 55% [15], we have noticed shared common mutations among several Qatari tribes and families causing a founder effect due to inbreeding which is worth further exploration in future research studies.

In our study, we were also able to show the prevalence of BRCA mutations among breast cancer patients of non-Qatari ethnicity including those of Arabs and non-Arabs ethnicity which is estimated to be 3.5%. This is similar to the reported prevalence of BRCA mutations among breast cancer patients in the general population [13]. It is believed however, that this prevalence is under-estimated due to the high cost of genetic testing and the difficulty in tracing non-Qatari's affected family members who most of them live abroad.

With the recent establishment of BRCA genetic testing at our CAP accredited lab at Hamad Medical Corporation on 2015 and its availability for all eligible patients at no cost, it is believed that the prevalence of BRCA mutations is going to be increased in the coming few years especially among non-Qatari patients. We also believe that with higher the awareness about our service, it is expected that the number of referrals will be significantly increased and more high risk families will be identified.

5. Limitations

One of the limitations of this study is that there was no accurate information on the number of patients who refused to pursue genetic testing. As a result, it was difficult to calculate the uptake of genetic testing among our patient cohort.

6. Conclusions and Recommendations

In this study, we described our experience with the hereditary and high risk clinic with a great focus on hereditary breast and ovarian cancers. The hereditary cancer and high risk clinic is a unique service that offers genetic counseling, risk assessment and risk reducing strategies to patients and their families who are at risk for hereditary or non-hereditary cancers. From our experience, we show that BRCA mutations are prevalent among those who are assessed to be high risk especially in those affected with breast cancer. We also showed that the prevalence of BRCA mutations is high especially among breast cancer patients of Qatari ethnicity which we believe is due to consanguinity and inbreeding and due to logistical reasons like coverage of genetic testing cost. It was estimated that the prevalence of BRCA mutations is approximately 3.5 % among women with breast cancer patients of non-Qatari ethnicity. This number is believed to be underestimated due several reasons including the high cost of genetic testing in the past, difficulties of reaching affected family members who live outside Qatar. We also believe that the prevalence of BRCA mutations among Qatari and non-Qatari's patients is underestimated due to social stigma and taboo about cancer and hereditary risks especially among Qatari's and Middle Eastern patients which might lead some individuals to be under psychological distress and hesitant to pursue genetic testing. In addition, patient's and health care provider's lack of awareness about our existing service and not referring high some risk families to our clinic could have impacted the true prevalence of BRCA mutations in the Qataris and non-Qatari's patients. However, due to the cancer genetics team effort in raising awareness on hereditary cancers, we have been getting a lot of referrals recently and the demand on our service is getting significantly higher.

In alignment with the Qatar's National Cancer Framework 2017-2022 which was launched with its motto of "Achieving Excellence in Cancer care: A vision for 2022" [16], framework healthcare systems are expected to deliver improved outcomes for cancer patients, to pursue excellence in cancer care, focusing on patient engagement, capturing greater data, ensuring better coordination of services, intervening earlier to reduce the cost, moving care to less complex healthcare settings and continuing to develop a specialist workforce. Our service is considered unique that is targeted toward cancer prevention and personalized medicine for high risk individuals and was highlighted at Qatar's national cancer framework 2017-2022 under the domain of prevention [16]. Since the establishment of the hereditary cancer and high risk clinic on 2013, we were able to expand our service to include gastrointestinal and other hereditary cancer syndromes. In addition, we were able to collaborate with the HMC lab to establish the BRCA genetic testing in house which will help in detecting more BRCA positive families in the future. In addition with the recent advances in genetic testing, we were able to introduce multigene panel testing at our clinic, we believe that it will provide us with new perspective on hereditary breast and ovarian cancers as well as on other hereditary syndromes as well.

Our service is an example of a multidisciplinary and well-established service targeted toward achieving excellence in cancer care through offering prevention and personalized medicine and that goes in line with Qatar's 2022 vision of achieving excellence in cancer care. The cancer genetics program is the first of its kind in the Middle East that puts HMC as a leader and innovator in patient- and family-centered care, acting as a model for other countries in the Middle East to follow to enhance patient's care in the region.

Acknowledgment

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Contributors

SB, HB, RA designed and supervised the study and were involved in data collection, statistical analysis, interpretation of data and writing manuscript. HG was mainly involved in the stage of statistical analyses. All authors approved the final version of this manuscript.

Ethics Committee Approval: Ethics committee approval was received for this study.

Competing interests: We have no financial interest to declare

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