The potential benefits of genetic testing in breast and ovarian cancer

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ABSTRACT

This article reviews some of the recent molecular aspects of breast/ovarian tumorigenesis, addresses the application of BRCA1 and BRCA2 mutations as predictive markers, and discusses the benefits and limitations of the approach of molecular testing of the malignancy. The efficacy and controversy around the option of prophylactic surgery for affected women is also discussed. Apparently, the most significant advantage of genetic testing is the increased awareness of women, of high-risk families and carriers of BRCA1 and/or BRCA2 mutations, with the importance of periodic medical examination. Analysis of some recent data of breast/ovarian cancers among the female population of Saudi Arabia shows low onset age, low frequency and diagnosis at late stages of malignancy. The potential of molecular testing for diagnostic and counselling purposes in breast/ovarian cancers in this community is presented.

Keywords: Breast/ovarian cancers, molecular testing.

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Breast cancer is known to be the most common malignancy among women internationally, with the Kingdom of Saudi Arabia being no exception. A positive family history is one of the major known risk factors for the disease. It has been estimated that 5%-10% of all breast cancer cases may be hereditary, caused by mutated predisposing genes. The inheritable type of breast cancer is characterized by an early age of onset, bilateral, an autosomal dominant mode of inheritance and association with other cancers. For example, a woman whose mother or sister had bilateral breast tumor has a higher lifetime risk of developing breast cancer than the one whose mother or sister had unilateral breast cancer. In the countries of North America and Europe, breast tumors are estimated to afflict one woman out of eight in her life time. Both hormonal and environmental factors, in addition to genetic factors, have been shown to play a role in the pathogenesis of breast cancer. It is known that the incidence of breast cancer varies in different ethnic groups. In relation to the high figures of North America and Europe, significantly lower figures were reported for other populations, e.g. in India and Japan. Statistics from the Middle East similarly show lower incidence rates, although breast cancer in this region of the world has been shown to comprise the highest relative frequency rate of all cancer types.

This paper aims to throw some light on the molecular tumorigenesis of breast/ovarian cancers, discuss the benefits and limitations of the approach of molecular diagnosis, and briefly present the options available to women who are carriers of BRCA1 and BRCA2 mutations. Molecular testing of the malignancies can potentially enhance earlier detection and help in achieving the ultimate goal of improving the diagnosis, management or prevention of the disease. Analysis of the features and frequency of specific cancers in a certain population are considered useful in understanding the role of some of the factors that determine the process of malignant-transformation. We have chosen to focus...
on some recent features of breast/ovarian cancers in the female population of Saudi Arabia. The present work is meant to increase the awareness with the role of the genetic component in breast/ovarian tumorigenesis. The topic of genetic predisposition to breast/ovarian cancers in the Saudi community has not been studied before.

**Genetic susceptibility to breast/ovarian cancers.** At the beginning of this decade, before the BRCA1 and BRCA2 genes were identified, several genes had been recognized as responsible for susceptibility to breast cancer. Germline mutations in the p53 gene on chromosome 17p caused a wide range of neoplasms including early-onset breast cancer, sarcomas, brain tumors, leukemias, and adrenocortical cancer. Epidemiological studies have suggested that heterozygotes for mutations in the ataxia telangiectasia gene (AT) on chromosome 11q are also at elevated risk of breast cancer. However, it is now apparent that mutations in the p53 and AT genes can only be responsible for a small proportion of the breast cancer cases that are not linked to BRCA1. By contrast, the 2 tumor suppressor genes, BRCA1 and BRCA2, that have been identified by Miki and colleagues in 1994 and by Wooster and co-workers in 1995, were found to account for a high proportion of inherited breast cancer. Approximately 5% of breast cancers and 10% of ovarian cancers in the United States are accounted for by mutations in BRCA1 and BRCA2 genes.

Susceptibility to breast cancer is inherited as an autosomal dominant trait, whereas the allele generally behaves as a recessive allele in somatic cells. On average, half of the offspring of a parent with BRCA1 mutation will inherit the same mutation and the females will be at high risk of breast cancer. A study by a special family linkage consortium in the United States showed that the effects of BRCA1 mutations were not limited to breast cancer but rather extended to increased risk of cancer at a variety of other sites, the most noticeable of which was the ovary. An estimate based on the family data contributed to the linkage consortium showed that the life time risk of breast cancer for BRCA1-mutation carriers was 73% by age 50 years and 87% by age 70 years, and the risk of ovarian cancer was 29% by age 50 years and 44% by age 70 years. These estimates were obtained from high-risk families and may not accurately reflect the real risks in the general population. Strenuous and associates have recently estimated from the analysis of 3318 Ashkenazi Jewish volunteers that the life-time risk to develop cancer in carriers of particular BRCA1 and BRCA2 mutations may reach 56% by the age of 70 for breast cancer, 16% for ovarian cancer and 16% for prostate cancer. This confirms that the risks to mutation carriers are high, but suggesting that they are not as high as estimated from linkage studies in selected high-risk families. Among female BRCA2-mutation carriers in the United States, the risks of breast cancer were estimated by Schubert and colleagues as 32% by age 50 years, 67% by age 70 years and 80% by age 90 years, thus yielding a life time risk similar to that of BRCA1 as reported by the US linkage consortium, but with higher ages at onset. In Schubert’s study BRCA2 families also included multiple cases of cancer of the male breast, ovary, fallopian tube, pancreas, urinary-bladder and prostate. BRCA1 mutations were detected in 33 families, BRCA2 mutations in 6 families, and in neither gene in 9 families. This finding led the authors to suggest that there is at least one other BRCA gene. Support for the existence of a further breast cancer susceptibility gene also comes from the study by Vehmanen et al of 100 Finnish breast cancer families of whom only 21% harbored a detectable BRCA1 or BRCA2 mutation, and linkage to these loci was excluded in a significant proportion of the Finnish multi-case families. Some mutations in BRCA1 are clearly associated with extremely high risks of cancer, but this does not mean that all mutations will have the same risk. It seems that genetic testing is particularly useful in families where the high risk of cancer is proven. It has been estimated that between 1 in 2000 and 1 in 500 in the general population carry high risk mutations in BRCA1. In a very recent study supported by the Federal German Breast Cancer Consortium, the families with members at risk of developing breast/ovarian cancers in Germany are considered to comprise 4 categories according to the number and onset age of the affected individuals. The criteria of family history determine the category as follows: (A) Three or more women, of any age, who have breast cancer. (B) At least 2 affected women, of any age, with both breast and ovarian cancers. (C) Two affected women; one woman diagnosed with unilateral breast cancer before the age of 50 years, or one woman with bilateral breast cancer diagnosed before the age of 40 years. (D) One woman with breast cancer diagnosed before the age of 30 years, or with ovarian cancer diagnosed before the age of 40 years. It has been observed that about 50% of the German female patients belonged to the categories A and B and about 50% of affected women belonged to the C categories. We believe that it is reasonable to consider these family history criteria in the definition of high-risk families in other populations.

In view of the facts that certain BRCA1 and BRCA2 mutations are population-specific and that the public awareness about breast cancer is increasing, an increasing demand for genetic testing is created. However, it could be appropriate that population-based screening for inherited susceptibility to breast and ovarian cancer may not be given a priority at present. An analysis of the
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interest and implications of genetic testing for the common BRCA1 mutation 185delG in the Ashkenazi Jewish population showed that 94% requested testing. The major reasons were concern for their own and that of their children’s risk and desire to know about the available surveillance options. The most prominent reason for declining the testing was concern about the health insurance. Because all identified carriers reported at least one 1st or 2nd degree relative with a history of breast or ovarian cancer, it was concluded that screening for susceptibility to breast and ovarian cancer is most appropriate for individuals with a positive personal or positive family cancer history.3

Role of BRCA1 and BRCA2 allele mutations in breast/ovarian tumorigenesis. The work on cancer cell mutations now provides strong evidence for the concept that in carcinogenesis the loss or alteration of the suppressor gene is at least as important as oncogene activation. Therefore, investigation of these genetic changes is not just a matter of academic interest. The cancers in which they occur include the most frequent cancers of the lung, colon and breast, which together account for about 40% of all human malignancies. Identification of the mutations underlying these cancers may aid
faster growth rate than sporadic tumors. Since the clinical and mammographic examinations at present do not detect premalignant lesions, it may be difficult to convince these women of the usefulness of the surveillance options available to them. However, offering 2 mammograms per year may help to alleviate some of the anxiety for the women who are carriers of BRCA1 or BRCA2 gene mutations.

In the absence of other preventive options the women at high-risk may seek prophylactic surgery. There is indeed little data from the literature that demonstrates the efficacy of prophylactic mastectomy. However, current surgical technique does not include complete removal of all breast tissue in prophylactic total mastectomy. Since a germline mutation will be present in all residual tissue, individuals may remain at increased risk following surgery. Similarly, prophylactic oophorectomy does not guarantee total protection from ovarian carcinoma, since there is a low incidence of peritoneal malignancies following oophorectomy. Estimates of the frequency of peritoneal carcinoma in high-risk women ranges from 2% to 25%. In women with a documented BRCA1 mutation, prophylactic oophorectomy at the completion of childbearing, or at the time of menopause is recommended by the American College of Obstetrics and Gynecology. It seems that prospective studies with a well-defined population of BRCA1 and BRCA2 mutation carriers are needed to delineate the protective efficacy of both prophylactic mastectomy and oophorectomy. High-risk women interested in prophylactic mastectomy or oophorectomy should be provided with information regarding the lack of evidence for or against risk reduction by this procedure. At present, the aggressive approach of prophylactic surgery remains somewhat controversial. Both retrospective and long term follow-up studies of mutation carriers are being undertaken to address the question of risk reduction by prophylactic surgery.

Recent data of breast/ovarian cancers in Saudi Arabia. About 60% of the Saudi nationals are in the age group lower than 20 years (Saudi Department of Statistics, 1994 Census). Hence the Saudi population is described as being a 'young' nation with a high rate of consanguineous marriages ranging from 52% to 68%. In general, reports from cancer registries in this country are scarce. Until recently no nationally coordinated registries existed. The earliest reports on the incidence of cancer in Saudi Arabia were published in the 1960s, 1970s, 1980s and 1990s. None of these statistics were population-based; they were rather hospital-based registries and as such they were not an accurate representative of the community. Nonetheless the data is useful as it provides valid information on the proportion of the various types of cancers. According to the newly established Saudi National Cancer Registry (NCR) the total number of all cancers reported in 1994 in Saudi females was 2247 and 2797 in Saudi males; these figures correspond to crude incidence rates (CIR) of 34 and 42 per 100,000. This CIR is computed by dividing the average yearly frequency of cancer cases by the corresponding population and multiplying the quotient by a base of 100,000. Among non-Saudi residents of Saudi Arabia, the total number of all cancer cases reported in 1994 was 825 in females and 1152 in males, giving a mean CIR, for both males and females, of 43 per 100,000. This CIR is apparently higher than the mean CIR reported among Saudis (38); a possible reason for the discrepancy is the fact that non-Saudis in Saudi Arabia are mainly working age groups. Registration of the cancer cases within the Saudi hospitals is prone to error; due to the undocumented referral or movement of cases to larger medical centers inside the country or abroad, inaccuracy in the registration of cancer cases is currently unavoidable. Relatively little data on the incidence of breast cancer in Saudi Arabia has been reported in the last decade.

An example of these reports is the analysis of breast cancer registries of 1987 and 1988 from all 22 hospitals in the Eastern Region of Saudi Arabia, undertaken by Al-Tamimi and colleagues. A total of 97 cases of breast cancer in females were registered, two thirds of whom were Saudis. The CIR per 100,000 population per year was 6 for Saudi and 17 for non-Saudi females. The age standardized incidence rate (ASR) of Saudi females was the lowest on the international scale of ASRs of breast cancer. The mean age of the patients with breast cancer was 43 and 44 years for Saudi and non-Saudi women. Breast cancer, together with lung cancer, shared the 2nd position as leading causes of death from cancer among Saudi females; each was responsible for 10% of the total deaths from cancer.

In order to gain a recent view of the data of breast and ovarian cancers in this country, we have used the 3 sources of recent information which are available. First, data which we compiled by recording breast cancer cases of women attending King Fahad University Teaching Hospital in Khobar in the period from January 1987 till August 1998, and ovarian cancer cases attending the Maternity and Children Hospital in Dammam in the period from June 1997 till August 1998. Second is the breast and ovarian cancer registry of the Saudi Aramco Medical Services Organization (SAMSO) for the period 1987 till 1995. Saudi Aramco oil company provides comprehensive medical service to a definite population living mainly in the Eastern Region of Saudi Arabia, amongst whom it becomes possible to calculate, with a reasonable degree of confidence, incidence rates of cancer. The third source of information is the recently established Saudi National Cancer Registry (NCR) of all cancer cases in 1994 from the entire country; this data was
Table 1 - Frequency and stage of malignancy at diagnosis of breast cancer among women of Saudi Arabia.

<table>
<thead>
<tr>
<th>Source of data and period of collection</th>
<th>This study* 1987-1998</th>
<th>SAMSO64 1987-1998</th>
<th>Saudi NCR63 1994</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saudi</td>
<td>Non Saudi</td>
<td>Saudi</td>
</tr>
<tr>
<td>Number of cases</td>
<td>134</td>
<td>95</td>
<td>136</td>
</tr>
<tr>
<td>Mean onset age (years)</td>
<td>50</td>
<td>48.6</td>
<td>nd</td>
</tr>
<tr>
<td>Relative Frequency Rate (%)</td>
<td>nd</td>
<td>nd</td>
<td>25.0</td>
</tr>
<tr>
<td>Crude Incidence Rate per 100,000</td>
<td>4.5</td>
<td>15.8</td>
<td>13.0</td>
</tr>
<tr>
<td>Stage at diagnosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-situ</td>
<td>3.0%</td>
<td>4.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Local</td>
<td>26.0%</td>
<td>46.0%</td>
<td>36.0%</td>
</tr>
<tr>
<td>Regional</td>
<td>42.5%</td>
<td>40.0%</td>
<td>52.0%</td>
</tr>
<tr>
<td>Distant</td>
<td>28.0%</td>
<td>10.5%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.9%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

* = Based on data collected at King Fahad University Teaching Hospital in Kohbar
nd = Not determined
SAMSO = Saudi Arabian Medical Services Organization
Saudi NCR = Saudi National Cancer Registry

published in 1996. Despite the limitation of not offering singly an accurate picture of breast/ovarian epidemiology, combining the information from all 3 sources enabled complementation of the data and provided a recent frequency data of the tumors in this country. An analysis of the recent trends of the frequency of breast/ovarian cancers among the female residents of Saudi Arabia shows overall mean onset ages of 50 and 44 years for breast and ovarian cancers (Tables 1 & 2). Apparently, there seem to be some increase in the mean onset age as compared with the values reported in this country about 10 years ago.65,67 In addition, the present data indicates younger onset ages of these cancers as compared to the corresponding ages observed in Western countries.68 Interestingly, in Caucasians, there is some proof that the mean onset age is lower in breast cancer patients from high-risk-families than in those with sporadic breast cancer. Marcus and co-workers,69 for example, have shown that the mean onset age of women with a BRCA1 mutation was 42.8±11.3 years, of women with other forms of familial breast cancer it was 47±14.6 years and of women with sporadic breast cancer it was 62.9±13.8 years. Whether a similar trend exists among the female population of Saudi Arabia obviously remains to be investigated.

The relative frequency rate (RFR) of breast cancer ranged from about 19% to 25% with no evidence of difference between Saudi and non-Saudi women. The RFR is defined as the percent frequency of each type of cancer relative to the overall frequency of

Table 2 - Frequency and stage of malignancy at diagnosis of ovarian cancer among women of Saudi Arabia.

<table>
<thead>
<tr>
<th>Source of data and period of collection</th>
<th>This study* 1987-1998</th>
<th>SAMSO64 1987-1998</th>
<th>Saudi NCR63 1994</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saudi</td>
<td>Non Saudi</td>
<td>Saudi</td>
</tr>
<tr>
<td>Number of cases</td>
<td>26</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>Mean onset age (years)</td>
<td>41.0</td>
<td>44.0</td>
<td>nd</td>
</tr>
<tr>
<td>Relative Incidence Rate (%)</td>
<td>nd</td>
<td>nd</td>
<td>4.5</td>
</tr>
<tr>
<td>Crude Frequency Rate per 100,000</td>
<td>5.0</td>
<td>10</td>
<td>nd</td>
</tr>
<tr>
<td>Stage at diagnosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-situ</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Local</td>
<td>61.5%</td>
<td>80.0%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Regional</td>
<td>23.0%</td>
<td>20.0%</td>
<td>35.0%</td>
</tr>
<tr>
<td>Distant</td>
<td>15.0%</td>
<td>0.0%</td>
<td>59.0%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

* = Based on data collected at King Fahad University Teaching Hospital in Kohbar
nd = Not determined
SAMSO = Saudi Arabian Medical Services Organization
Saudi NCR = Saudi National Cancer Registry
cancer from all sites. According to our data and that of the Saudi NCR, the crude incidence rate (CIR) averaged 5.5 and 15.0 per 100,000 among the Saudi and non-Saudi women. These figures are very close to the above-mentioned CIRs (5.8 & 17.2) reported by Al-Tamimi et al.57 The higher CIR is explained by the fact that a higher proportion of the non-Saudi women living in Saudi Arabia belong to the working age group and hence are more prone to the disease. The highest (of all 3 registries) mean CIR of breast cancer among Saudi women is 13.4 as reported by SAMSO,68 and the age-related CIRs are 3.3 among the 20-29 age group, 33.7 among the 30-39 age group, 51.6 among the 40-49 age group, 53.2 among the 50-59 age group, and 32.9 per 100,000 among older than 60 years. Thus the incidence rates seem to decline after menopause. By comparison in the USA the mean CIR is 105 for white females; the rates among the 40-49 year old being 156 per 100,000.70 Our registry of the frequency of ovarian cancer among Saudi and non-Saudi women, given in Table 2, shows an overall mean onset of age 44 years. The RFR is slightly higher in Saudi women (4.5%) as compared to the non-Saudis (3.8%). The CIR of ovarian cancer for Saudi women ranged from 5.2 to 1.5 per 100,000 hence it was lower than the CIR for non-Saudi women, i.e. 10.0 per 100,000. This finding is similar to the above mentioned finding with regard to breast cancer and could be explained by the same reason. The recent UNICEF demographic indicators point out that Saudi Arabia has one of the highest total fertility rates in the world.71 Multiparity and increased pregnancy in early adulthood, which are observed among Saudi women, are likely to confer protection against breast/ovarian cancers. Thus the relatively low crude incidence rates of breast and ovarian cancers in this country could be partly explained. Furthermore, according to the 1994 Census, the number of Saudi females in the age group of less than 19 years comprised 59% of the total female population, those in the age group 20 to 59 comprised 36%, and the over 60 years of age comprised only 5% of the female population in this society. Identical percentages of age distribution were also recorded for the male population. Therefore, the low crude incidence rates of breast/ovarian cancers can possibly be attributed to the factor of age distribution of the Saudi society that has a large proportion (59%) of children and young people.

The stage of malignancy at diagnosis were classified according to the SEER® system of classification. It was apparent that, with the exception of the SAMSO registry for non-Saudi women, the percentage of breast cancer cases diagnosed at the in-situ stage were generally low, relative to the international figures, and did not exceed 4.2% of the cases in both Saudi and non-Saudi women. Although the majority of both Saudi and non-Saudi breast cancer cases were diagnosed at the local and regional stages, a sizable proportion of the Saudi cases were diagnosed at the distant stage; the percentages ranged from 10.0% to 28.4% for Saudis and from 1.0% to 10.5% for non-Saudis. Hence the Saudi breast cancer cases showed a tendency to be diagnosed at the late distant stage more than the non-Saudi ones. Our data shows that among Saudi women a significant percentage of ovarian cancer cases tend to be diagnosed at the distant stage, i.e. 15.4%. This tendency is even more prominent in both the SAMSO and Saudi NCR registries where more of the Saudi cases were diagnosed at the distant stage with percentages of 59% and 43.9%. We have also observed that the stage of malignancy at diagnosis of ovarian cancer among non-Saudi women was mainly at the local stage (80%) and the rest of the cases were diagnosed at the regional stage (20%). It was also interesting to observe that in all 3 registries none of the ovarian cancer cases were diagnosed at the in situ stage. In summary, the incidence of breast/ovarian cancers in Saudi females is characterized by young age, low crude incidence rates, rarity of diagnosis at the in situ stage and high proportion of diagnosed cases at late stages of malignancy.

Potential benefits of genetic testing in breast/ovarian cancer in Saudi Arabia. Generally, classical medical care for patients with breast and ovarian cancers is easily accessible in most of the major medical centers of Saudi Arabia. The diagnostic facilities available in this country are quite adequate and they include routine medical examination, mammography, fine-needle aspiration and other advanced histo-pathological techniques. However, genetic testing for assessment of predisposition to breast/ovarian cancers is presently not offered. The spectrum of treatment services offered include lumpectomy, mastectomy with or without breast reconstruction, chemotherapy and/or radiotherapy. In the etiology of breast/ovarian cancers, the environmental component, like the case of many other cancers, is known to play an important role. This fact has been adequately proven by many population-migration studies. Genetic predisposition to breast/ovarian cancers is known to account for about one tenth of the disease cases and this factor is highlighted in detail in this article. In addition, the effect of intake of oral contraceptives is debatable although some authorities maintain that it has a role to play in breast/ovarian tumorigenesis.

The introduction of genetic testing for breast/ovarian cancers in this community is advocated for several reasons. Genetic testing is essential for offering genetic counseling to members of families affected with the inherited type of breast/ovarian cancer. The anxiety of women with positive family history of breast/ovarian cancers is naturally immense because they consider themselves at high

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risk of developing the disease. This profound worry could be partly alleviated through offering those who wish to know, explicit knowledge whether they are BRCA1/BRCA2 mutation carriers, and the specific nature and linkage of the mutations to malignancy. Women with high risk of developing the disease, by virtue of being carriers of known predisposing genetic variants, could be educated on the particular importance of periodic medical examination and mammography. Furthermore, if detection of some of the breast/ovarian cancers among the female population of this country could be achieved at earlier stages, this will represent a desirable goal. Some progress in this direction is expected to be made by introduction of novel diagnostic techniques such as the genetic testing. Forthcoming work by this research group is dedicated to investigate the genotype/phenotype relationships of the disease and linkage studies in patients from this region who are BRCA1/BRCA2 mutation carriers. The results of such studies should facilitate application of genetic testing of breast/ovarian cancers in this community.

In conclusion, the molecular bases of breast/ovarian tumorigenesis, including the potential benefits of genetic testing, have been reviewed. The potential of molecular testing of breast/ovarian cancers in this community should not be ignored. Increasing the awareness with the importance of periodic clinical examinations is a significant benefit of the molecular testing for women at risk of developing breast/ovarian cancers especially those with inherited susceptibility to the disease. Molecular testing is also favored as it may facilitate diagnosis at an earlier stage of malignancy, is useful in offering genetic counselling to members of affected families and may influence the choice of the intervention measures.

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