Prevalence of \textit{BRCA1} and \textit{BRCA2} Mutations Among High-Risk Saudi Patients With Breast Cancer

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\textbf{Purpose} Over the past three decades, the incidence rate of breast cancer (BC) among Arab women has continually increased. However, data on the prevalence of \textit{BRCA1}/\textit{2} mutations are scarce. Although the population in Saudi Arabia is at large homogeneous and consanguinity is common, especially in the central, eastern, and southern regions of the country, the prevalence of \textit{BRCA1} and \textit{BRCA2} mutations and the characteristics of BC are not well studied in the country.

\textbf{Methods} This prospective observational study intended to determine the prevalence of \textit{BRCA1} and \textit{BRCA2} mutations and sought to examine the clinicopathologic features of BC associated with these mutations.

\textbf{Results} Of 310 patients, 270 (87\%) had no mutation. \textit{BRCA} mutations were identified in 40 patients; \textit{BRCA1} mutations were found in 11\% of patients, and \textit{BRCA2} mutations were found in 2\% of patients. Variants of unknown significance were found in 15\% of patients (45 patients). Triple-negative BC (TNBC) accounted for 86\% of all patients with BC and mutations. The following three recurrent deleterious founder \textit{BRCA1} mutations were observed: c.4136_4137delCT was observed in five unrelated patients, c.5530delC was observed in three unrelated patients, and c.4524G>A mutations were observed in five unrelated patients. One novel mutation was identified in the \textit{BRCA1} gene (c.5512 dup [p.Glu1838Glyfs*42]).

\textbf{Conclusion} Among high-risk Saudi patients with BC, \textit{BRCA1} mutations are prevalent (11\%). TNBC is the most common BC subtype. Furthermore, age alone does not have a significant association with mutation, but a combination of risk factors such as age, familial history, and TNBC has a significant association with \textit{BRCA} mutation.

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frequent than BRCA1 mutations in the Asian population. Population-specific mutations have also been described among Ashkenazi Jews as well as patients of Spanish ancestry. Founder BRCA1 and BRCA2 mutations have also been found in several European populations in Austria, Slovenia, Italy, France, Spain, Portugal, Belgium, the Netherlands (Holland), Germany, Czech Republic, Slovakia, Hungary, Greece, Cyprus, Denmark, Sweden, Norway, Finland, Iceland, the United Kingdom, Ireland, Poland, Latvia, Lithuania, Estonia, Belarus, and Russia. Although the population in Saudi Arabia is overall homogeneous and consanguinity is common, especially in the central, eastern, and southern regions of the country, the prevalence of BRCA1 and BRCA2 mutations and the characteristics of BC are not well studied. Available data are conflicting and inconclusive because they are based on retrospective analyses of small heterogeneous Saudi and non-Saudi patients. Given these considerations, the main objectives of this study were to determine the prevalence and founder effect of BRCA1 and BRCA2 mutations in Saudi patients with BC and to study the clinicopathologic features of BC associated with these genetic mutations.

**METHODS**

**Study Design**

This prospective observational study enrolled patients between October 2010 and September 2016 at King Abdulaziz Medical City, Riyadh, Saudi Arabia. The study was approved by the Institutional Review Board of King Abdullah International Medical Research Center (RC12/158/R) and conducted in compliance with the International Conference on Harmonization Good Clinical Practice guideline.

**Eligibility and Enrollment**

Patients with BC with at least one of the following high-risk criteria were eligible for the study: a first-degree relative with a known mutation in a cancer susceptibility gene; two or more BC primary tumors in a single family member; two or more individuals with breast cancer primary tumors on the same side of family with at least one family member diagnosed at age ≤ 50 years; ovarian cancer; male breast cancer; first- or second-degree relative with breast cancer at age ≤ 45 years; triple-negative BC (TNBC) at age < 60 years; and bilateral BC. After meeting the previously mentioned criteria, the patient or the substitute decision maker was approached for consent.

**Informed Consent**

The study protocol and the informed consent were approved by the Institutional Review Board of King Abdullah International Medical Research Center, King Abdulaziz Medical City.

**Blood Collection, DNA Extraction, and Quantification**

Approximately 3 mL of blood were collected in sterile tubes containing EDTA from all subjects enrolled onto the study. Genomic DNA was extracted following standard protocol and then screened for BRCA1 and BRCA2 mutations using next-generation sequencing. In addition, patients were screened for deletion or duplication genomic rearrangements within BRCA genes using multiple ligation probe amplification (MRC-Holland, Amsterdam, the Netherlands). Variants or mutations were validated by Sanger sequencing using specific polymerase chain reaction primers and sequenced on an ABI 3730 DNA Analyzer (Thermo Fisher Scientific, Waltham, MA). The blood samples were sent for testing at the Clinical Molecular and Personalized Diagnostics Unit at Catholic University and Hospital Foundations in Rome, Italy.

**Statistical Analysis**

Categorical variables are reported as numbers and frequencies. χ² and Fisher’s exact tests were performed as appropriate to assess any association between gene mutations and other parameters, with a two-sided significance level of 5%. The statistical analysis was carried out using IBM SPSS Statistics Version 22.0 (IBM, Armonk, NY).

**RESULTS**

**Patient Characteristics**

Seven hundred forty Saudi patients were diagnosed with BC during the study period, of whom 399 (46%) were eligible for genetic testing. However, 89 patients declined genetic testing for
various reasons. Thus, 310 patients were eligible for statistical analysis (Fig 1). Patient demographic characteristics are listed in Table 1.

In total, 302 patients (97.4%) were women and eight (2.6%) were men. Sixty-six patients (21.3%) were younger than age 45 years. One hundred three patients (33.2%) had a family history of breast cancer.

### Disease Characteristics

Almost half of the patients (n = 153; 49.3%) had a stage II BC, and TNBC was the most common molecular subtype (n = 126; 40.6%). Nine patients (2.9%) had bilateral BC, and invasive ductal carcinoma was the most common histology (n = 289; 93.2%; Table 2).

### BRCA Mutations

Of 310 patients, 270 (87.1%) had no mutations. BRCA1 or BRCA2 mutations were identified in 40 patients (12.9%), whereas variants of unknown significance were reported in 45 patients (14.5%). BRCA1 mutations (10.7%) were more prevalent than BRCA2 mutations (2.2%; Table 3).

Four patients with BC and one patient with BC and ovarian cancer were reported to be carriers of the recurrent mutation c.4136_4137delCT.
The five BCs had a triple-negative molecular profile and invasive ductal carcinoma histology; one patient had a family history of BC (first- and fourth-degree relatives). The c.4136_4137delCT (p.SER1379*) mutation accounted for 15% of BRCA1 mutations, and the c.4524G>A (p.Trp1508Ter*) mutation was reported in another five patients (15%). In addition, we identified an unreported mutation (c.5512 dup [p.Val1838Glyfs*42]) in one family (mother and

| Characteristic | No. of Patients | %  |
|----------------|----------------|----|
| Clinical stage |                |    |
| I              | 46             | 14.8 |
| II             | 153            | 49.3 |
| III            | 67             | 21.6 |
| IV             | 39             | 12.6 |
| Not available  | 5              | 1.6  |
| Laterality     |                |    |
| Unilateral     | 301            | 97.1 |
| Bilateral      | 9              | 2.9  |
| Molecular subtype* |  |    |
| TNBC           | 126            | 40.6 |
| Luminal B      | 81             | 26.1 |
| Luminal A      | 64             | 20.7 |
| HER2 enriched  | 38             | 12.3 |
| Unknown        | 1              | 0.3  |
| Histotype      |                |    |
| Invasive (or infiltrating) ductal carcinoma | 289 | 93.2 |
| Invasive lobular carcinoma | 14 | 4.5 |
| Other          | 7              | 2.23 |

Abbreviations: TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2; *Luminal A indicates estrogen receptor and progesterone receptor positive, HER2 negative, Ki-67 < 14%, and grade 1; luminal B indicates estrogen receptor and/or progesterone receptor positive and either HER2 positive or HER2 negative with high level of Ki-67 (> 14%); TNBC indicates hormone receptor negative (estrogen receptor and progesterone receptor negative); and HER2 enriched indicates estrogen receptor and progesterone receptor negative and HER2 positive.

| Table 3. Prevalence of BRCA1 and BRCA2 Mutations |
|------------------------------------------------|
| **BRCA1** | No. of Patients | %  | **BRCA2** | No. of Patients | %  |
| Mutation status |  | | | | |
| Positive | 33 | 10.7 | 7 | 2.2 |
| Negative | 267 | 86.1 | 268 | 86.5 |
| Variant of unknown significance | 10 | 3.2 | 35 | 11.3 |
| Total | 310 | 100 | 310 | 100 |
| Molecular subtype* |  | | | | |
| Luminal A | 1 | 3.0 | 1 | 14.3 |
| Luminal B | 1 | 3.0 | 2 | 28.6 |
| TNBC | 31 | 93.9 | 4 | 57.1 |
| Total | 33 | 99.9 | 7 | 100 |

Abbreviation: TNBC, triple-negative breast cancer.

*Luminal A indicates estrogen receptor and progesterone receptor positive, HER2 negative, Ki-67 < 14%, and grade 1; luminal B indicates estrogen receptor and/or progesterone receptor positive and either HER2 positive or HER2 negative with high level of Ki-67 (> 14%); and TNBC indicates hormone receptor negative (estrogen receptor and progesterone receptor negative).
A daughter with TNBC. The daughter was diagnosed first, at 28 years old, and the mother was diagnosed 2 years later (Table 4).

Disease-associated BRCA2 mutations were reported in seven patients, but none were identified more than once (Table 5). Forty-five patients (14.5%) had mutations of unknown significance; the majority were in BRCA3 (Table 6).

### Correlation of BRCA1 Gene Mutation With Different Parameters

We determined the correlation between BRCA1 gene mutations and different molecular subtypes and found that TNBC is highly associated with BRCA1 mutations ($P < .001$) and family history of BC ($P < .001$) but that young age alone ($\leq 45$ years old, $P = .358$) was not associated

| BRCA Gene Mutation | No. of Patients (n = 33) | % | Characteristic |
|--------------------|--------------------------|---|----------------|
| c.4136_4137delCT (p.SER1379*) | 5 | 15.2 | 4 patients with BC and 1 patient with BC and ovarian cancer |
| c.4524G>A (p.Trp1508Ter*) | 5 | 15.2 | 3 unrelated families, 2 patients with BC (1 with BC and ovarian cancer) |
| c.5152+1G>C (IVS18+1G>T) | 3 | 9.1 | — |
| c.5251C>T (p.Arg1751*) | 3 | 9.1 | 3 members of 1 family (3 sisters), of whom 1 has BC |
| c.5530delIC p.Leu1844Serfs | 3 | 9.1 | 3 unrelated patients with BC |
| c.5512 dup (p.Val1838Glyfs*42) novel | 2 | 6.1 | 2 members of 1 family (mother and 1 daughter), both affected with BC |

1326_1327insG | 1 | 3.0 | — |
| c.1066C>T | 1 | 3.0 | — |
| c.1140dup | 1 | 3.0 | — |
| c.124delA (p.Ile42Tyrfs*) | 1 | 3.0 | — |
| c.1953delGAAA (p.Lys653Serfs*47) | 1 | 3.0 | — |
| c.1961dup (p.Tyr655Valfs*18) | 1 | 3.0 | — |
| c.4065_4068delTCAC (p.Asn1355_Gln1356?fs) | 1 | 3.0 | — |
| c.4524A>T (p.Gly1508Gly) | 1 | 3.0 | — |
| c.4609C>T (p.Gln1537*) | 1 | 3.0 | — |
| c.4676-2A>G | 1 | 3.0 | — |
| c.5030_5033del (p.Thr1677Ilefs*2) | 1 | 3.0 | — |
| c.5074+2T>A | 1 | 3.0 | — |

Abbreviation: BC: breast cancer.

### Table 5. Characteristics of Patients With BRCA2 Gene Mutation

| BRCA Gene Mutation | No. of Patients (n = 7) | % | Characteristic |
|--------------------|--------------------------|---|----------------|
| 7643delAT | 1 | 14.3 | Hormone-positive breast cancer, age < 45 years |
| c.2808_2811 | 1 | 14.3 | Positive family history and TNBC |
| c.5034_504del | 1 | 14.3 | TNBC, age < 45 years |
| c.6591_6592delTG | 1 | 14.3 | Hormone-positive breast cancer |
| c.8332_1G>T | 1 | 14.3 | TNBC, positive family history |
| c.9502_131G>A | 1 | 14.3 | TNBC, positive family history |
| c.968_971 | 1 | 14.3 | HER2-positive disease, age < 45 years |

Abbreviations: HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.
with significant risk (Table 7). Overall, the BRCA mutation rate was significantly higher with two or more risk factors than with a single risk factor.

**DISCUSSION**

Little is known about the molecular analysis of BRCA1 and BRCA2 and etiologic factors of BC in Saudi Arabia. To our knowledge, the current study is the first prospective study in the country for BRCA testing in selected high-risk Saudi patients with BC. It showed that 12.9% of selected high-risk patients with BC had BRCA deleterious mutations, similar to frequencies reported from Lebanon but higher than frequencies reported from Qatar. In our study, BRCA1 mutations were more common (82.5% of mutations) than BRCA2 mutations, which is similar to the pattern in the Western population, although different from that among Asian populations, in which BRCA2 mutations are more common.

Three recurrent deleterious BRCA1 mutations (c.4136_4137delCT, c.5530delC, and c.4524G>A) were identified. Likewise, a recent retrospective study published in 2016 reported three recurrent BRCA1 mutations (c.1140dupG, c.4136_4137delCT, and c.5530delC) in 818 unselected patients with BC from different ethnicities in Saudi Arabia. These patients were diagnosed with primary BC between 1990 and 2011 and had their files and samples selected from another major medical and research center in the country (King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia).

The current study identified an unreported mutation in BRCA1 (c.5512dupG) in two patients with BC from one family, a 28-year-old daughter and her mother diagnosed 2 years apart, both with TNBC. This novel mutation, along with other reported founder mutations in Saudi Arabia, may contribute to the potentially disease-associated etiology of BC in Saudi Arabia. Such knowledge is also important for cost-effective genetic testing strategies for BRCA1/2 gene mutations.

In our study, TNBC accounted for 85% of BCs in all patients with mutations (93.9% in patients with BRCA1 mutations and 57.1% in patients with BRCA2 mutations), which is consistent with the literature because TNBC is the predominant molecular profile in patients with a germline BRCA1 mutations. Importantly, the literature reports similarity in gene expression profiles between TNBC and BC in women with BRCA1 mutations. In addition, the current study shows that the frequency of BRCA mutation was significantly higher with two or more risk factors than one risk factor, which is comparable to the results of a local study conducted among patients with BC from different ethnicities and international studies. TNBC was the most important risk factor, followed by family history and young age. In addition, our results agree with data from international studies demonstrating that BRCA mutations are influenced by a TNBC molecular profile. Similar observations have been made with respect to young age, and the frequency of BRCA mutations seems to be increased in patients diagnosed at a young age.

**Table 6. Variants of Unknown Significance**

| Gene Mutation (VUS) | No. of Patients | %     |
|---------------------|----------------|-------|
| BRCA1               |                |       |
| 964G>C              | 1              | 10    |
| c.1286C>A           | 1              | 10    |
| c.1088A>G           | 1              | 10    |
| c.1396C>G           | 1              | 10    |
| c.2393C>G           | 1              | 10    |
| c.301+55G>A         | 2              | 20    |
| c.305+55G>A         | 1              | 10    |
| c.4787C>A           | 1              | 10    |
| c.5087T>C           | 1              | 10    |
| BRCA2               |                |       |
| 301+55G>A           | 1              | 2.9   |
| 4185+22_4185+23insTG| 1              | 2.9   |
| 4994A>G             | 1              | 2.9   |
| c.1012G>A           | 2              | 5.7   |
| c.122C>T            | 7              | 20    |
| c.2329G>A           | 1              | 2.9   |
| c.266C>T            | 1              | 2.9   |
| c.3367A>G           | 2              | 5.7   |
| c.517-4C>G          | 1              | 2.9   |
| c.7207A>G           | 1              | 2.9   |
| c.7445C>A           | 1              | 2.9   |
| c.7534C>T           | 5              | 14.3  |
| c.7628A>G           | 4              | 11.4  |
| c.7976+23C>T        | 1              | 2.9   |
| c.8452G>T           | 1              | 2.9   |
| c.8632+2T>C         | 1              | 2.9   |
| c.9875C>T           | 3              | 8.6   |
| IVS20+2T>C          | 1              | 2.9   |
Finally, our study identified novel BRCA mutations and their predictors and risk factors. Such mutations seem to be specific for Saudi patients because different mutations are described in patients from Lebanon and North Africa.23 Our study also highlights challenges and limitations for BRCA testing in Saudi Arabia and possibly the whole Arab region. These include lack of a database for the Arab population, scarcity of local central laboratories and shortage of genetic counselors (only six genetic counselors are available in Saudi Arabia), social barriers to individuals’ acceptance, lack of awareness among patients and clinicians, and cost of testing. Therefore, future goals in Saudi Arabia are guided toward improving the strategy for genetic testing in BC. This strategy includes developing a cost-effective BRCA testing panel, creating a national and regional database, recruiting more genetic counselors, identifying high-risk patients for preventive services, and establishing an effective awareness and educational program. Additional efforts consist of implementing universal genetic screening guidelines in which a TNBC molecular profile and young age would be added as criteria. There was also a high rate of variants of unknown significance (87.5%) in our cohort, as well as other studies published from the region,21,24,33 and reporting these variants is important because some of them might be classified as pathogenic variants in the future.

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Table 7. Correlation of BRCA1 Gene Mutation With Different Parameters

| Factor                      | Positive | Negative | P*   |
|-----------------------------|----------|----------|------|
| Factor                      | No. of Patients | %   | No. of Patients | %   |      |
| Age, years                  |          |         |      |          |      |
| ≤ 45                        | 28       | 9.3     | 208  | 69.3     | .358 |
| > 45                        | 5        | 1.7     | 59   | 19.7     |      |
| Family history of BC        |          |         |      |          | .001 |
| No                          | 12       | 4.0     | 188  | 62.7     |      |
| Yes                         | 21       | 7.0     | 79   | 26.3     |      |
| TNBC                        |          |         |      |          | .001 |
| Yes                         | 30       | 10.0    | 93   | 31.0     |      |
| No                          | 3        | 1.0     | 174  | 58.0     |      |

Abbreviations: BC: breast cancer; TNBC, triple-negative breast cancer.

* Two-sided significance level set at 5%.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. World Cancer Research Fund International: Breast cancer statistics. http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/breast-cancer-statistics
2. Kurian AW: BRCA1 and BRCA2 mutations across race and ethnicity: Distribution and clinical implications. Curr Opin Obstet Gynecol 22:72-78, 2010
3. Brown R, Kerr K, Haoudi A, et al: Tackling cancer burden in the Middle East: Qatar as an example. Lancet Oncol 13:e501-e508, 2012
4. Saint-Germain MA, Longman AJ: Breast cancer screening among older Hispanic women: Knowledge, attitudes, and practices. Health Educ Q 20:539-553, 1993
5. Al-Saad S, Mahmood Shamsi N: Risk factors of breast cancer in Bahrain. Bahrain Med Bull 31:1-11, 2009
6. Miller AB: Screening for breast cancer in the Eastern Mediterranean Region. East Mediterr Health J 16:1022-1024, 2010
7. Balmaña J, Diez O, Rubio IT, et al: BRCA in breast cancer: ESMO clinical practice guidelines. Ann Oncol 22:vi31-vi34, 2011 (suppl 6)
8. Easton DF: How many more breast cancer predisposition genes are there? Breast Cancer Res 1:14-17, 1999
9. Campeau PM, Foulkes WD, Tischkowitz MD: Hereditary breast cancer: New genetic developments, new therapeutic avenues. Hum Genet 124:31-42, 2008
10. Adam MP, Ardinger HH, Pagon RA, et al (eds): BRCA1- and BRCA2-associated hereditary breast and ovarian cancer, in GeneReviews. Seattle, WA, University of Washington, 1993
11. Antoniou A, Pharoah PD, Narod S, et al: Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: A combined analysis of 22 studies. Am J Hum Genet 72:1117-1130, 2003
12. Chen S, Parmigiani G: Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 25:1329-1333, 2007
13. Hall MJ, Reid JE, Burbidge LA, et al: BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer. Cancer 115:2222-2233, 2009
14. Kim H, Choi DH: Distribution of BRCA1 and BRCA2 mutations in Asian patients with breast cancer. J Breast Cancer 16:357-365, 2013
15. Fackenthal JD, Olopade OI: Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations. Nat Rev Cancer 7:937-948, 2007
16. Janavičius R: Founder BRCA1/2 mutations in the Europe: Implications for hereditary breast-ovarian cancer prevention and control. EPMA J 1:397-412, 2010
17. El-Harith HA, Abdel-Hadi MS, Steinmann D, et al: BRCA1 and BRCA2 mutations in breast cancer patients from Saudi Arabia. Saudi Med J 23:700-704, 2002
18. Alshatwi AA, Shaf G, Hasan TN, et al: Single nucleotide polymorphisms in the p21 and bcl2 cancer susceptibility genes and breast cancer risk in Saudi Arabia. Asian Pac J Cancer Prev 12:2607-2610, 2011
19. Al-Moghrabi N, Al-Qasem AJ, Aboussekhra A: Methylation-related mutations in the BRCA1 promoter in peripheral blood cells from cancer-free women. Int J Oncol 39:129-135, 2011
20. Alanazi M, Pathan AA, Abduljaleel Z, et al: Association between PARP-1 V762A polymorphism and breast cancer susceptibility in Saudi population. PLoS One 8:e85541, 2013
21. Hasan TN, Shafi G, Syed NA, et al: Lack of association of BRCA1 and BRCA2 variants with breast cancer in an ethnic population of Saudi Arabia, an emerging high-risk area. Asian Pac J Cancer Prev 14:5671-5674, 2013
22. Bu R, Siraj AK, Al-Obaisi KA, et al: Identification of novel BRCA founder mutations in Middle Eastern breast cancer patients using capture and Sanger sequencing analysis. Int J Cancer 139:1091-1097, 2016
23. Robertson L, Hanson H, Seal S, et al: BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years. Br J Cancer 106:1234-1238, 2012
24. Bujassoum S, Bugrein HA, Al-Sulaiman R: Genotype and phenotype correlation of breast cancer in BRCA mutation carriers and non-carriers. J Cancer Sci Ther 9:358-362, 2017
25. Foulkes WD, Smith IE, Reis-Filho JS: Triple-negative breast cancer. N Engl J Med 363:1938-1948, 2010
26. Blows FM, Driver KE, Schmidt MK, et al: Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: A collaborative analysis of data for 10,159 cases from 12 studies. PLoS Med 7:e1000279, 2010
27. Wong-Brown MW, Meldrum CJ, Carpenter JE, et al: Prevalence of BRCA1 and BRCA2 germline mutations in patients with triple-negative breast cancer. Breast Cancer Res Treat 150:71-80, 2015
28. Malone KE, Daling JR, Doody DR, et al: Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. Cancer Res 66:8297-8308, 2006
29. Spurdle AB, Couch FJ, Parsons MT, et al: Refined histopathological predictors of BRCA1 and BRCA2 mutation status: A large-scale analysis of breast cancer characteristics from the BCAC, CIMBA, and ENIGMA consortia. Breast Cancer Res 16:3419, 2014
30. Metcalfe K, Gershman S, Lynch HT, et al: Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. Br J Cancer 104:1384-1392, 2011
31. Hartman AR, Kaldate RR, Sailer LM, et al: Prevalence of BRCA mutations in an unselected population of triple-negative breast cancer. Cancer 118:2787-2795, 2012
32. Kwon JS, Gutierrez-Barrera AM, Young D, et al: Expanding the criteria for BRCA mutation testing in breast cancer survivors. J Clin Oncol 28:4214-4220, 2010
33. Saudi Cancer Registry: Cancer incidence and survival report Saudi Arabia 2007. https://nhic.gov.sa/eServices/Documents/Incidence%20Report%202007.pdf