Prevalence of germline TP53 mutation among early onset middle eastern breast cancer patients

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Abstract

Background: The data on prevalence and clinical relevance of TP53 germline mutations in early onset Middle-Eastern breast cancer (BC) is limited.

Methods: We determined TP53 germline mutations in a cohort of 464 early onset BC patients from Saudi Arabia using capture sequencing based next generation sequencing.

Results: Germline TP53 pathogenic mutations were found in 1.5% (7/464) of early onset Saudi BC patients. A total of six pathogenic missense mutations, one stop gain mutation and two variants of uncertain significance (VUS) were detected in our cohort. No TP53 pathogenic mutations were detected among 463 healthy controls. TP53 mutations carriers were significantly more likely to have bilateral breast cancer (p = 0.0008). At median follow-up of 41 months, TP53 mutations were an unfavorable factor for overall survival in univariate analysis. All the patients carrying TP53 mutations were negative for BRCA1 and BRCA2 mutations. Majority of patients (85.7%; 6/7) carrying TP53 mutation had no family history suggestive of Li-Fraumeni Syndrome (LFS) or personal history of multiple LFS related tumors. Only one patient had a positive family history suggestive of LFS.

Conclusions: TP53 germline mutation screening detects a clinically meaningful risk of early onset BC from this ethnicity and should be considered in all early onset BC regardless of the family history of cancer, especially in young patients that are negative for BRCA mutations.

Keywords: TP53 mutation, Breast cancer, Li-Fraumeni syndrome, Lifetime risk

Background

TP53 (RefSeq NM_000546.6) mutations with Li-Fraumeni syndrome (LFS) is an autosomal dominant inherited disease primarily associated with high-risk for wide variety of early onset neoplasms [1]. TP53 gene mutations are present in up to 2-6% of breast cancer (BC) patients younger than 35 [2–5]. The National Cancer Institute reported a cumulative cancer incidence of 50% by age of 31 years among female carriers of TP53 germline mutations [6]. Despite the establishment of known criteria to diagnose LFS [7], TP53 mutation carriers have been reported in a large number of patients who have not fulfilled these criteria. De novo mutations in TP53 are well-documented and the incidence could reach up to 20% [8]. Accessibility to next generation sequencing have helped in identifying TP53 germline mutations in individuals who do not fulfill clinical criteria previously recommended for LFS testing [9, 10].

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In Saudi Arabia, BC is the most common cancer affecting women and it accounts for about 30% of all cancers diagnosed in women [11]. Interestingly, median age of diagnosis of BC among Saudi women is 50 years [11, 12], which is 10 years younger than those from western population [13–15]. Therefore, exploring the inherited germline mutations in cancer predisposition genes such as TP53 is of great importance in this population.

However, data on the frequency of TP53 germline mutations in young Saudi BC patients is limited [16]. To address this issue, in the current study, we screened 464 young Saudi breast cancer patients for TP53 germline mutation. We investigated the prevalence and spectrum of TP53 mutations in the entire cohort regardless of the family history and investigated the clinico-pathological characteristics of TP53 mutation carriers.

Methods
Patient samples and data collection
Four hundred and sixty-four patients with early-onset breast cancer diagnosed between 1990 and 2015 at King Faisal Specialist Hospital and Research Centre (KFSHRC) were included in the study. Patients presenting with only ductal carcinoma in-situ were not included. Detailed clinico-pathological data, including follow-up data, were noted from case records and have been summarized in Table 1. Family history was collected from case records or by telephonic interview. 2019 World Health Organization (WHO) classification of breast tumors was used to classify the histologic subtype of each breast tumor sample. Overall survival was defined as the length of time from the date of diagnosis, that patients diagnosed with the disease are still alive. As controls, we analyzed a cohort of 463 age and gender matched cancer-free individuals for whom exome sequencing data was available in local population database. All the individuals of the control cohort were of the same ethnicity. Institutional Review Board of KFSHRC provided ethical approval for the current study. Research Advisory Council (RAC) granted waiver of informed consent for use of retrospective patient case data under project RAC# 2140 008. The patient samples were de-identified by assigning a unique number to each sample which could not be traced back to the individual patient. All the methods were carried out in accordance with relevant guidelines and regulations.

DNA isolation
DNA samples were extracted from formalin-fixed and paraffin-embedded non-tumor tissues utilizing Gentra DNA Isolation Kit (Gentra, Minneapolis, MN, USA) according to the manufacturer’s protocols as elaborated in the previous studies [17]. The non-tumor tissues were selected from normal tissues adjacent to the tumor tissue or from normal tissues from other organ sites operated for an unrelated disease. The normal tissues were confirmed by histopathological examination.

Targeted capture sequencing and mutation calling
Targeted capture sequencing was performed on 464 breast cancer samples using Illumina platform. Pre-alignment quality metrics were obtained using FastQC (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/) and quality passed sequencing reads were aligned to the human reference genome hg19 using Burrows-Wheeler Aligner (BWA) [18]. Local realignment was performed and PCR duplicates were marked using Picard tools (http://broadinstitute.github.io-picard/). In order to obtain high quality mutation calls, base-quality recalibration and variant calling was performed with GATK [19]. Post alignment quality metrics were obtained using GATK. The identified variants were annotated using ANNOVAR [20]. TP53, BRCA1 and BRCA2 variants with a minor allele frequency of greater than 0.001 as found in dbSNP, the National Heart, Lung, and Blood Institute exome sequencing project, 1000 Genomes and Exome Aggregation Consortium (ExAC) were excluded for further analysis. A variant was considered a true positive if the variant allele frequency (VAF) was at least 20% with sequencing depth in the variant location region to be >=20. All the mutations were also manually checked using the Integrated Genomics Viewer (IGV) to filter out artifacts. The control group included 463 cancer-free women age less than 40 years for whom whole exome sequencing (WES) data was available. TP53 mutations were extracted from WES and similar filters and pathogenicity classification was applied.

Pathogenicity of variants
All the variants were classified according to The American College of Medical Genetics and Genomics (ACMG) guidelines for TP53 gene [21]. Further, variants were also scored for likelihood of pathogenicity using Combined Annotation Dependent Depletion (CADD) [22], Align GVG D [23] and BayesDel [24]. VUSs according to ACMG were considered likely pathogenic if predicted pathogenic by two of the three prediction tools.

Mutation validation by PCR and sanger sequencing
To validate the mutations identified by Capture sequencing technology, Primer 3 software was used to design the primers for each mutation (available upon request). PCR was performed in a total volume of 25 µl with 20 ng of genomic DNA, 2.5 µl 10 x Taq buffer, 2.3 mM dNTPs, 1 unit Taq polymerase and 0.2 µM each primer and de-ionized water. The efficiency and quality of the amplified PCR products was confirmed by loading them on a 2% agarose gel.
For Sanger sequencing, the PCR products were subsequently subjected to direct sequencing with BigDye terminator V 3.1 cycle sequencing reagents and analyzed on an ABI 3730XL DNA analyzer (Applied Biosystems, Foster City, CA). Reference sequences were downloaded from NCBI GenBank. Sequencing traces were analyzed with the Mutation Surveyor v4.04 (Soft Genetics, LLC, State College, PA).

**Table 1 Clinico-pathological variables for the patient cohort (n=464)**

| Clinico-pathologic variables | n (%) |
|------------------------------|-------|
| **Age (years)**              |       |
| ≤30                          | 77 (16.6) |
| 31 - 40                      | 387 (83.4) |
| Median (in years)            | 36.0 |
| Range(IQR)^                  | 32.0 – 39.0 |
| **Family history of breast cancer** |       |
| Yes                          | 55 (11.9) |
| No                           | 409 (88.1) |
| **Family history of any cancer** |       |
| Yes                          | 91 (19.6) |
| No                           | 373 (80.4) |
| **Personal history of other cancer** |       |
| Yes                          | 5 (1.1) |
| No                           | 459 (98.9) |
| **Bilateral breast cancer**  |       |
| Yes                          | 4 (0.9) |
| No                           | 460 (99.1) |
| **Histological type**        |       |
| Infiltrating Ductal carcinoma| 421 (90.7) |
| Infiltrating Lobular carcinoma| 19 (4.1) |
| Mucinous carcinoma           | 10 (2.2) |
| Others                       | 14 (3.0) |
| **Tumor size**               |       |
| ≤2 cm                        | 137 (29.5) |
| >2 cm                        | 311 (67.1) |
| Unknown                      | 16 (3.4) |
| **Lymph node status**        |       |
| Negative                     | 164 (35.4) |
| Positive                     | 284 (61.2) |
| Unknown                      | 16 (3.4) |
| **Distant metastasis**       |       |
| Absent                       | 411 (88.6) |
| Present                      | 37 (8.0) |
| Unknown                      | 16 (3.4) |
| **Histologic Stage**         |       |
| I                            | 71 (15.4) |
| II                           | 170 (36.6) |
| III                          | 170 (36.6) |
| IV                           | 37 (8.0) |
| Unknown                      | 16 (3.4) |
| **Histologic Grade**         |       |
| Well differentiated           | 29 (6.3) |
| Moderately differentiated     | 190 (40.9) |

**Table 1 Clinico-pathological variables for the patient cohort (n=464) (Continued)**

| Clinico-pathologic variables | n (%) |
|------------------------------|-------|
| Poorly differentiated        | 218 (47.0) |
| Unknown                      | 27 (5.8) |
| **Estrogen Receptor**        |       |
| Positive                     | 268 (57.7) |
| Negative                     | 196 (42.3) |
| **Progesterone Receptor**    |       |
| Positive                     | 238 (51.3) |
| Negative                     | 226 (48.7) |
| **Her-2 neu**                |       |
| Positive                     | 176 (37.9) |
| Negative                     | 288 (62.1) |
| **Molecular subtype**        |       |
| Luminal                      | 303 (65.3) |
| Her-2 positive               | 73 (15.7) |
| Triple negative              | 88 (19.0) |
| **BRCA1mutation**            |       |
| Present                      | 41 (8.8) |
| Absent                       | 423 (91.2) |
| **BRCA2mutation**            |       |
| Present                      | 16 (3.4) |
| Absent                       | 448 (96.6) |
| **Survival Duration (in months)** | Median 55.1 |
| Range(IQR)^                  | 27.0 – 79.0 |

^ IQR, inter quartile range

Tissue microarray (TMA) construction and immunohistochemistry (IHC) staining

TMA construction was performed as described earlier [25]. Briefly, tissue cylinders with a diameter of 0.6 mm were punched from representative tumor regions of each donor tissue block and brought into recipient paraffin block using a modified semiautomatic robotic precision instrument (Beecher Instruments, Woodland, WI). Two cores of breast cancer were arrayed from each case.
IHC staining was performed manually with staining and scoring of estrogen receptor (ER), progesterone receptor (PR) and Her-2 neu performed as described previously [26]. Briefly, the cutoff for ER and PR was taken as 1% nuclear staining, whereas HER2 overexpression was assessed according to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines [27].

**Statistical analysis**

The associations between clinico-pathological variables and TP53 mutation was performed using contingency table analysis and Fisher exact test. Mantel-Cox log-rank test was used to evaluate overall survival. Survival curves were generated using the Kaplan-Meier method. Cox proportional hazards regression model was used for multivariate analysis. Two-sided tests were used for statistical analyses with a limit of significance defined as p value < 0.05. Data analysis was performed using the JMP14.0 (SAS Institute, Inc., Cary, NC) software package.

**Results**

**TP53 mutations and their clinico-pathological characteristics**

In our cohort, a total of nine mutations were identified in early onset Saudi BC patients by Capture sequencing and further validated by Sanger sequencing technology. Seven of these mutations were found pathogenic/likely pathogenic (1.5%, 7/464) and other two as variants of uncertain significance (VUS) by ACMG guidelines for TP53 gene [21]. One VUS was predicted pathogenic by all three prediction tools whereas other was predicted pathogenic by only CADD. Most of the mutations observed in TP53 gene were missense (six mutations) along with one stop gain mutation (Table 2). However, none of the pathogenic mutations in TP53, BRCA1 and BRCA2 were detected among 463 matched healthy controls. Due to the limitation of Capture sequencing technology, large mutations (>300 – 400 base pairs) cannot be identified.

Median age of the TP53 mutant cases was 32 years (range: 22 – 39 years) at the time of diagnosis. Of the patients harboring TP53 mutation, 2 (28.6%) patients underwent modified radical mastectomy, 4 (57.1%) had simple mastectomy and 1 (14.3%) had lumpectomy. All the seven tumors were of infiltrating ductal carcinoma histologic subtype. Two (28.6%) patients presented with grade 2 tumor, whereas five (71.4%) patients had grade 3 tumors. Lymph node metastasis was noted in two (28.6%) patients and distant metastasis was present in three (42.9%) patients. Two (28.6%) patients presented with stage II tumor, two (28.6%) with stage III and three (42.9%) with stage IV tumors. Bilateral breast cancer was present in two (28.6%) patients. One (14.3%) patient had triple negative breast cancer. Family history was positive in one (14.3%) patient; with malignancies noted in five first degree relatives (rhabdomyosarcoma, cerebellar astrocytoma, osteosarcoma, oligodendroglioma and pancreatic cancer). Three (42.9%) patients received neoadjuvant chemotherapy and all the patients received adjuvant chemotherapy. Four (57.1%) patients received radiotherapy. All the seven cases were negative for BRCA1/2 mutations (Supplementary table S1).

Median follow-up for the seven patients was 41 months (range: 25 – 50 months). During the follow-up, one patient developed local recurrence as well as liver metastasis and died due to disease progression (survival = 50 months). Another patient died after 25 months of follow-up due to disease progression, with metastasis involving the brain. The remaining five patients were alive at the time of last follow-up (Supplementary table S1).

**Table 2** Mutation classification according to ACMG TP53* guidelines and computational predictions

| Chr | Position | Ref | Alt | Amino Acid | Type | CADD | aGVGD | BayesDel | ACMG_TP53 | Alt Depth | Total Depth | VAF |
|-----|----------|-----|-----|-----------|------|------|------|---------|-----------|-----------|------------|------|
| 17  | 7,579,890| T   | A   | p.Q5L     | Missense | 6.003 | Class C0 | 0.197777 | Likely Pathogenic | 40 | 94 | 42.6 |
| 17  | 7,577,121| G   | A   | p.R273C  | Missense | 25.5 | Class C65 | 0.433271 | Likely Pathogenic | 256 | 510 | 50.2 |
| 17  | 7,577,094| G   | A   | p.R282W  | Missense | 26   | Class C65 | 0.542691 | Likely Pathogenic | 693 | 1400 | 49.5 |
| 17  | 7,577,022| G   | A   | p.R306X  | Stop gain | 37 | NA | 0.625005 | Pathogenic | 186 | 549 | 33.9 |
| 17  | 7,573,988| C   | T   | p.A347T  | Missense | 27.2 | Class C0 | 0.152476 | VUS | 195 | 421 | 46.3 |
| 17  | 7,578,508| C   | T   | p.C141Y  | Missense | 23.8 | Class C65 | 0.561428 | Likely Pathogenic | 917 | 2904 | 31.6 |
| 17  | 7,577,548| C   | T   | p.G245S  | Missense | 28.9 | Class C55 | 0.550935 | Pathogenic | 202 | 464 | 43.5 |
| 17  | 7,577,538| C   | T   | p.R248Q  | Missense | 28.6 | Class C35 | 0.377622 | Pathogenic | 170 | 193 | 88.1 |
| 17  | 7,577,093| C   | A   | p.R282L  | Missense | 27.5 | Class C65 | 0.416469 | VUS | 56 | 125 | 44.8 |

*TP53 RefSeq NM_000546.6

Note: For aGVGD, Class C15 and higher are considered pathogenic; for BayesDel, scores ≥ 0.16 are considered pathogenic; for CADD, scores ≥ 20 are considered pathogenic.
Table 3: Summary of clinico-pathological variables in TP53 mutant breast cancer patients age ≤ 40 years, after excluding BRCA carriers (n = 407)

| Clinico-pathological variables                  | TP53 carriers (n = 7) | TP53 non-carriers (n = 400) | p value |
|------------------------------------------------|----------------------|----------------------------|---------|
| **Age at diagnosis, years**                     |                      |                            |         |
| Mean ± SD                                       | 32.0 ± 6.0           | 34.9 ± 4.6                 | 0.2410  |
| Median (range)                                  | 32 (22 – 39)         | 36 (13 – 40)               | 0.1380  |
| ≤30                                             | 3 (4.7)              | 61 (95.3)                  | 0.0813  |
| 31 – 40                                         | 4 (1.2)              | 339 (98.8)                 |         |
| **Family history of breast cancer**            |                      |                            |         |
| Yes                                             | 0 (0.0)              | 42 (100.0)                 | 1.0000  |
| No                                              | 7 (1.9)              | 358 (98.1)                 |         |
| **Family history of any cancer**               |                      |                            |         |
| Yes                                             | 1 (1.4)              | 71 (98.6)                  | 1.0000  |
| No                                              | 6 (1.8)              | 329 (98.2)                 |         |
| **Personal history of other cancer**           |                      |                            |         |
| Yes                                             | 0 (0.0)              | 4 (100.0)                  | 1.0000  |
| No                                              | 7 (1.7)              | 396 (98.3)                 |         |
| **Bilateral breast cancer**                     |                      |                            |         |
| Yes                                             | 2 (66.7)             | 1 (33.3)                   | 0.0008* |
| No                                              | 5 (1.2)              | 399 (98.8)                 |         |
| **Tumor size**                                  |                      |                            |         |
| ≤2 cm                                           | 1 (0.8)              | 120 (99.2)                 | 0.4441  |
| >2 cm                                           | 6 (2.2)              | 264 (97.8)                 |         |
| **Lymph node status**                           |                      |                            |         |
| Negative                                        | 3 (2.2)              | 134 (97.8)                 | 0.6996  |
| Positive                                        | 4 (1.6)              | 250 (98.4)                 |         |
| **Distant metastasis**                          |                      |                            |         |
| Absent                                          | 4 (1.1)              | 355 (98.9)                 | 0.0139* |
| Present                                         | 3 (9.4)              | 29 (90.6)                  |         |
| **Stage**                                       |                      |                            |         |
| I                                               | 0 (0.0)              | 63 (100.0)                 | 0.0481* |
| II                                              | 2 (1.4)              | 144 (98.6)                 |         |
| III                                             | 2 (1.3)              | 148 (98.7)                 |         |
| IV                                              | 3 (9.4)              | 29 (90.6)                  |         |
| **Histologic Grade**                            |                      |                            |         |
| Well differentiated                              | 0 (0.0)              | 28 (100.0)                 | 0.3018  |
| Moderately differentiated                       | 2 (1.1)              | 174 (98.9)                 |         |
| Poorly differentiated                           | 5 (2.8)              | 173 (97.2)                 |         |
| **Estrogen receptor status**                    |                      |                            |         |
| Positive                                        | 4 (1.6)              | 246 (98.4)                 | 1.0000  |
| Negative                                        | 3 (1.9)              | 154 (98.1)                 |         |
| **Progesterone receptor status**                |                      |                            |         |
| Positive                                        | 3 (1.4)              | 217 (98.6)                 | 0.7078  |
| Negative                                        | 4 (2.1)              | 183 (97.9)                 |         |
| **Her-2 neu status**                            |                      |                            |         |
Clinico-pathological associations of TP53 mutation carriers

We analyzed the association between TP53 mutation and clinico-pathological characteristics among 407 BC patients (after excluding BRCA mutant cases). We found a significant association between TP53 mutation and patients with bilateral breast cancer ($p = 0.0008$) as well as distant metastasis ($p = 0.0139$). Importantly, TP53 mutations were associated with poor overall survival ($p = 0.0003$) (Table 3; Fig. 1). However, on multivariate analysis, TP53 mutations were not an independent predictor of overall survival.

Discussion

The prevalence of TP53 mutations among women with early breast cancer has been explored in different populations [2, 28–31]. The accessibility to gene panel testing and next generation sequencing, in addition to the updated international guidelines which downplay the importance of positive family history of LFS [32, 33], have led to dramatic increase in TP53 testing, especially among young BC patients. Therefore, we conducted this study to determine the TP53 germline mutation in a large cohort of 464 Saudi women diagnosed with BC <40 years of age.

We found germline TP53 mutation in 1.5% (7/464) of Saudi early-onset BC patients regardless the family history of cancer or personal history of multiple LFS-related tumors. None of these seven mutations appeared to be recurrent. All detected mutations were missense mutations except one, which was stop gain. No pathogenic mutations were found in the control cohort.

Table 3 Summary of clinico-pathological variables in TP53 mutant breast cancer patients age ≤ 40 years, after excluding BRCA carriers ($n = 407$) (Continued)

| Clinicopathological variables | TP53 carriers ($n = 7$) | TP53 non-carriers ($n = 400$) | p value |
|------------------------------|------------------------|-----------------------------|---------|
|                              | n (%)                  | n (%)                       |         |
| Positive                     | 3 (1.7)                | 169 (98.3)                  | 1.0000  |
| Negative                     | 4 (1.7)                | 231 (98.3)                  |         |
| Molecular Subtype            |                        |                             |         |
| Luminal                      | 4 (1.4)                | 274 (98.6)                  | 0.7464  |
| Her-2 positive               | 2 (2.9)                | 68 (97.1)                   |         |
| TNBC                         | 1 (1.7)                | 58 (98.3)                   |         |
| Overall survival (5-years)   | 33.3                   | 82.5                        | 0.0003* |

*, significant p value

Fig. 1 Survival Analysis of TP53 mutation in breast cancer. Kaplan Meier survival plot showing statistically significant poor overall survival in TP53 mutant cases compared to TP53 wild-type cases ($p = 0.0360$)

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The mutation rate in our study of 1.5% is lower than what other studies have reported where TP53 mutation rate ranges from 3 to 8% in very early onset BC [2, 4, 28]. Although, in our cohort we used the cut-off age of early onset BC <40 years, decreasing the cut-off age to very early onset of BC <30 years did not show enrichment of TP53 mutation as shown by others [4, 34, 35]. This could probably be due to ethnic differences in the prevalence among different population.

TP53 mutation carriers had a significantly worse overall survival than non-carriers. However, in multivariate analysis, this association was lost, which could partially be attributed to the small number of TP53 mutation carriers in this cohort.

In our previous study including same group of samples, we determined the frequencies of the most common inherited germline mutations, BRCA1 and BRCA2. Although we found BRCA1 prevalence of 8.8% and BRCA2 prevalence of 3.4% in the entire cohort, none of the TP53 germline mutation carriers were positive for BRCA1 or BRCA2 mutations. This is consistent with previous reports where TP53 mutations are seen in early-onset BC patients that are negative for BRCA1/2 pathogenic variants [30, 31, 36].

TP53 mutations carriers were more likely to have bilateral BC compared to non-carriers in our study. However, we did not find TP53 mutations to be associated with HER2 positive cancers. Several previous studies have shown that women carrying germline TP53 mutations were diagnosed with HER2 positive tumors [29, 37–39]. Among our mutation carriers, only three out of seven (42.9%) had HER2 (+3) receptor expression. Which indicates that HER2 amplification in Saudi population might not be a useful marker in identifying TP53 mutations. Recent large study conducted on Chinese population couldn’t identify the association between TP53 mutations and HER2 positivity in BC patients [34]. Whether the lack of association observed in our study is due to sample size or true reflection of ethnic difference in BC need to be further evaluated through additional studies.

An intriguing finding is that most of the TP53 mutation carriers have negative family or personal history of cancer. Only one patient met the criteria of LFS or LFL syndrome. This is of important clinical implications, given the socio-cultural barriers to accurately documenting family history of cancer and lack of early BC awareness make genetic testing of TP53 in young BC patient an important strategy to identify BC patient with hereditary BC.

Overall, our study has shown the spectrum of TP53 germline mutation in Saudi cohort. The differences in frequency of TP53 mutation, and clinical characteristics such as lack of TP53 enrichment at very early onset (<30 years of age) BC and the lack of association with HER2 status further suggest that TP53 carriers may vary across different ethnicities and countries. We therefore propose that women with breast cancer before the age of 40 to be screened for TP53 mutations even with no family history of cancer.

Understanding of TP53 mutation prevalence coupled with screening for these selected women will not only be beneficial for patients but also for their families by adopting specific surveillance options for early cancer detection and/or prevention. Furthermore, knowledge about TP53 mutation may aid clinician to the best treatment modalities for these patient such as bilateral mastectomy to reduce the risk of a second primary breast cancer and minimizing the radiotherapy if possible since radiation therapy may increase risks in these patients [40, 41].

Despite the relatively large sample size of early onset BC, this study has certain limitations. Firstly, this is a retrospective and a single tertiary care center study, so selection bias cannot be ignored. Secondly, the low power in statistical analyses performed due to small number of mutant positive cases should be considered cautiously when interpreting the results. Thirdly, the socio-cultural barriers in this population may preclude accurate documentation of family history.

Conclusions
In conclusion, TP53 germline mutation screening detects a clinically meaningful risk of early onset BC from this ethnicity and should be considered in all early onset BC regardless of the family history of cancer, especially in young patients that are negative for BRCA mutations.

Supplementary information
The online version contains supplementary material available at https://doi.org/10.1186/s13053-021-00206-w.

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Authors’ contributions
A.K.S., T.M., R.B. and K.I. designed the study, performed targeted capture sequencing analysis and helped write the manuscript. S.K.P. performed the immunohistochemical experiments and helped write the manuscript. S.A. analyzed the data. M.A. were involved in performing the experiments. D.A. provided the clinical resources and executed the study. A.T. and F.A. provided the clinical resources and executed of the study. K.S.A. designed the study, supervised the study and drafted the manuscript. All authors have reviewed and approved the final manuscript.

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Availability of data and materials
Not applicable.
Declarations

Ethics approval and consent to participate
Institutional Review Board of King Faisal Specialist Hospital and Research Centre provided approval for the collection of archival samples. For this study, since only archived paraffin tissue blocks and retrospective patient data were used, a waiver of consent was obtained from Research Advisory Council (RAC) under project RAC# 2140 008. This study was performed in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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